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Indik. odchylka	>>	>>	=	=	<<	=	<<	=	<<	=	=	=	=	=	=	=	=	=	=	=	=	=	=

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Práce s nadprahovou hodnotou podobnosti

Dok.	Citácia	Percento*
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[2520»] zlúčenín a určovania priorít je iteračný proces, ktorý zahŕňa pravidelnú revíziu prioritných zlúčenín v každej kategórii vždy, keď sa získajú nové informácie a/alebo spoľahlivejšie údaje alebo keď je k dispozícii spätná väzba z uplatňovaných opatrení na zníženie emisií (Dulio a von der Ohe (2013)). 17 Tabuľka 3.1:[«2520] Zoznam

2. odsek : **spoľahlivosť [83%]**

[1»] Vallejo, A. van Nuijs, V. Ware a M. Viklander. Making waves: Collaboration in the time of sars-cov-2 - rapid development of an international co-operation and wastewater surveillance database to support public health decision-making. Water Research, 199(1):1–7, 2021. C. T. Moermond, R. Kase, M. Korkaric a M. Ågerstrand. Cred: [«1] Criteria

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4. odsek : **spoľahlivosť [76%]**

[1»] Vallejo, A. van Nuijs, V. Ware, and M. Viklander. Making waves: Collaboration in the time of sars-cov-2 - rapid development of an international co-operation and wastewater surveillance database to support public health decision-making. Water Research, 199(1):1–7, 2021. 23 24 4. H. M. Taha, R. Aalizadeh, N. Alygizakis, J. Antignac, H.[«1] P. H.

5. odsek : **spoľahlivosť [77% - 79%]**

[559»] Dessau□Roßlau,[4»] Germany 8 Environmental Institute, Koš, Slovakia Full list of author information is available at the end of[7»] the article © The Author(s) 2020. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article[«559] are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativeco mmons. org/licenses/by/4.0/. Dulio et al.[«4] Environ Sci Eur (2020) 32:100 26 Page[«7] 2

6. odsek : **spoľahlivosť [88%]**

[538»] detailed feedback/material on specific activities. All authors have read, made comments and approved the final manuscript. Funding Not applicable. Availability of data and materials Not applicable. Ethics approval and consent to participate Not applicable. Consent for publication Not applicable. Competing interests The authors declare that they have no competing interests. Author details 1 INERIS, National Institute for Environment and Industrial Risks, Verneuil en Halatte,[«538] France.

7. odsek : **spoľahlivosť [100%]**

[2568»] ronmental Institute, Koš, Slovakia. 9 Department of Environmental Science, Stockholm University, Stockholm, Sweden. 10 Department of Aquatic Sciences and Assessment, SLU, Swedish University of Agricultural Sciences, Uppsala, Sweden. 11 National and Kapodistrian University of Athens, Athens, Greece.[«2568] 12 CSIC, Spanish

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21. odsek : **spoľahlivosť [96%]**

[2651»] Technology, VA-Teknik, 971 87, Luleå, Sweden b Department of Civil and Environmental Engineering and Nireas-International Water Research Centre, School of Engineering, University of Cyprus, PO Box 20537, 1678, Nicosia, Cyprus c Environmental Institute, Okruzna 784/42, 97241, Kos,**[«2651]** Slovakia d

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[2653»] Box 1751, Adelaide SA 5001, Australia x Division of Biological and Environmental Science and Engineering, Water Desalination and Reuse Center, King Abdullah University of Science and Technology (KAUST), Thuwal, 23955-6900, Saudi Arabia y Department of Chemistry, University of Bath, Bath,**[«2653]** UK z University

24. odsek : **spoľahlivosť [79%]**

[2488»] practice in wastewater surveillance. Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Acknowledgments All authors wish to thank the WWTP operators for providing **[«2488]**

25. odsek : **spoľahlivosť [76%]**

[1171»] (BEAGAL18/00042). TM wishes to thank the generous support of the Operational Program Integrated Infrastructure for the project "Strategic research in the field of SMART monitoring, treatment and preventive protection against coronavirus (SARS-CoV-2) ", Project no. 313011ASS8 (cofinanced by the European Regional Development Fund) and the project VIR-SCAN - Wastewater monitoring data as an early warning tool to alert COVID-19 in the population (EOSCsecretariat.eu has received funding from the European Union's Horizon Program call H2020-INFRAEOSC- 05-2018-2019, grant Agreement number 831644). SK (IBISS) acknowledges the financial support from Ministry**[«1171]** of

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37. odsek : **spoľahlivosť [77%]**

[4»] of Luxembourg, 6 Avenue du Swing, 4367 Belvaux, Luxembourg Full list of author information is available at the end of the article Mohammed Taha et al.**[«4]**

38. odsek : **spoľahlivosť [81% - 82%]**

[2346»] S36 and S63**[2409»]** (HPHA, SEH, MN, IS) were funded by the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) Project No. (FKZ) 3716 67 416 0, updates to S36 (HPHA, SEH, MN, IS) by the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protec tion (BMUV) Project No. (FKZ) 3719**[«2346]** 65 408**[«2409]** 0. MiK

39. odsek : **spoľahlivosť [87%]**

[1739»] csb.uni.lu/eci/pubchem). Declarations Ethics approval and consent to participate Not applicable. Consent for publication Not applicable. Competing interests The authors declare that they have no competing interests. Author details 1 Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxem bourg, 6 Avenue du Swing,**[«1739]** 4367 Belvaux,

40. odsek : **spoľahlivosť [93%]**

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41. odsek : **spoľahlivosť [100%]**

[2648»] Foundation, Staffelstrasse 10, 8045 Zurich, Switzerland. 23 Institute of Biogeochemistry and Pollutant Dynam ics, ETH Zurich, 8092 Zurich, Switzerland. 24 Eawag, Swiss Federal Institute for Aquatic Science and Technology, Überlandstrasse 133, 8600 Dübendorf, Switzerland.**[«2648]** 25 Thermo Fisher

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43. odsek : **spoľahlivosť [87%]**

[2543»] Hemlock Park Drive, Kingsport, TN 37663, USA. 33 State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sci ences, Chinese Academy of Sciences (SKLECE, RCEES, CAS), No. 18 Shuangqing Road, Haidian District, Beijing 100086, China. 34 Hope College, Holland, MI 49422, USA. 35 University**[«2543]** of California,

44. odsek : **spoľahlivosť [64% - 74%]**

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56. odsek : **spoľahlivosť [71%]**

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[575»] von der Ohe PC, Thomaidis NS (2017) Prediction of acute toxicity of emerging contaminants on the water flea Daphnia magna by Ant Colony Optimization-Support Vector Machine QSTR models. Environ Sci Processes Impacts 19:438–448. https://doi.o**[«575]**

58. odsek : **spoľahlivosť [78% - 79%]**

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60. odsek : **spoľahlivosť [100%]**

[575»] der Ohe, P.C., Thomaidis, N.S., 2017. Prediction of acute toxicity of emerging contaminants on the water flea Daphnia magna by ant colony optimization-support vector machine QSTR models. Environ. Sci. Process Impacts 19 (3), 438–448. Ahrens,**[«575]** L.,

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64. odsek : **spoľahlivosť [91%]**

Parliament and of the Council. 2022. Dasenaki, M.E., Thomaidis, N.S., 2015. Multi-residue determination of 115 veterinary drugs and pharmaceutical residues in milk powder, butter, fish tissue and eggs using liquid chromatography-tandem mass spectrometry. Anal. Chim. Acta 880, 103–121. Dulio, V., et al., 2020. The NORMAN Association and**[«2390]** the

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66. odsek : **spoľahlivosť [71% - 88%]**

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70. odsek : **spoľahlivosť [73%]**

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Kapitola 1
Úvod
Zber, spracovanie a analýza environmentálnych zlúčenín sú dôležité činnosti pri skúmaní a monitorovaní znečistenia a kvality životného prostredia. Tieto procesy umožňujú identifikovať prítomnosť a koncentráciu rôznych chemických zlúčenín v životnom prostredí, čo je dôležité pre ochranu verejného zdravia a ekosystémov. Stanovenie priorít v oblasti chemických znečisťujúcich zlúčenín je hlavnou výzvou pre environmentálnych manažérov a tých, ktorí prijímajú rozhodnutia, ale je nevyhnutné zamerať sa na zdroje, ktoré sú k dispozícii na zmierňujúce opatrenia.
Zoznam chemických zlúčenín, ktoré sú v literatúre často diskutované ako „emerging substances“, neustále rastie, pričom niektoré už sú v pokročilom štádiu hodnotenia a môžu sa čoskoro stať regulovanými. Je dôležité sa zaoberať aj zlúčeninami, o ktorých máme obmedzené informácie, a existujú aj neidentifikované novovznikajúce zlúčeniny, ktoré nie sú súčasťou monitorovacích programov. Nie je možné zaoberať sa všetkými týmito zlúčeninami rovnako podrobne. Musia sa identifikovať zlúčeniny s vysokou prioritou pre monitorovanie a/alebo hodnotenie rizika. Ak sú však použité konvenčné metodiky stanovenia priorít, veľká časť týchto nových zlúčenín by sa vyhodila alebo ponechala v pohotovostnom režime pre nedostatok údajov. Je preto dôležité rozhodnúť, ako by sa malo s týmito jednotlivými zlúčeninami zaobchádzať, pokiaľ ide o opatrenia, ktoré sa majú prijať na vyplnenie súčasných medzier. V roku 2010 bola preto zriadená pracovná skupina NORMAN pre stanovovanie priorít vznikajúcich zlúčenín s cieľom vypracovať schému stanovovania
priorít pre nové zlúčeniny, v ktorej sú chemikálie uprednostňované podľa potreby, pričom sa zohľadňujú súčasné medzery v poznatkoch (Dulio a von der Ohe (2013)).
NORMAN začala svoju činnosť v roku 2005 s finančnou podporou Európskej komisie (projekt NORMAN). V roku 2009 sa asociácia NORMAN stala stálou samostatne fungujúcou sieťou referenčných laboratórií, výskumných centier a súvisiacich organizácií pre monitorovanie nových environmentálnych zlúčenín. Bola zriadená ako neziskové združenie všetkých zainteresovaných strán zaoberajúcich sa vznikajúcimi environmentálnymi
1
1.1. PRÍNOSY PRÁCE
2
zlúčeninami. V súčasnosti má viac ako 90 členov. Slovensko v tejto organizácii zastupuje Environmental Institute a Výskumný ústav vodného hospodárstva.
1.1 Prínosy práce
Predkladaná habilitačná práca má za cieľ vytvoriť metodiku a implementáciu databázového systému, ktorý poskytuje komplexné informácie o zlúčeninách. Ide najmä o chemické zlúčeniny, ktorých prítomnosť ohrozuje ekosystém a životné prostredie. Vytvorené automatizované databázové riešenie zároveň tvorí základný stavebný kameň na ďalšie inovatívne aplikácie na posúdenie potenciálnej nebezpečnosti a rizík daných zlúčenín v životnom prostredí. Medzi tieto ďalšie aplikácie radíme:
• nasadenie umelej inteligencie (napr. formou strojového učenia) na spracovanie, vyhľadávanie a verifikáciu obrovského množstva údajov o chemických zlúčeninách z rôznych zdrojov,

• vytvorenie univerzálneho API (Application Programming Interface) rozhrania na prepojenie s inými databázovými systémami a ďalšie pokročilé spracovanie údajov.

Prínosy a ciele sumarizované v tejto habilitačnej práci môžeme formulovať nasledovne:

1. Vytvoriť centralizované riešenie na uchovávanie a výmenu informácií o chemických zlúčeninách, ktoré ovplyvňujú životné prostredie.
2. Vytvoriť databázové riešenie napojené na užívateľské rozhranie, ktoré poskytne užívateľom prístup k informáciám na celosvetovom poli, pričom má byť dodržaný princíp FAIR – (Findable, Accessible, Interoperable, Reusable).
3. Zabezpečiť po technickej stránke dlhodobú udržateľnosť databázového riešenia (napr. dbať na normálovú architektúru databázy, integritu vstupných údajov atď.)

Habilitačná práca je podložená 4 časopiseckými publikáciami, pričom publikácia Taha a kol. (2022) opisuje práve potrebu vytvorenia centralizovaného riešenia (Cieľ 1). V publikáciách Dulio a kol. (2020); Lundy a kol. (2021) je databázový systém opísaný ako platforma na rýchle zdieľanie údajov s otvoreným prístupom (Cieľ 2). Databázový systém pozostáva z rozsiahleho počtu vzájomne prepojených tabuliek, pričom objem informácií v ňom neustále narastá (Dulio a kol. (2020); Taha a kol. (2022)). Návrh celého databázového systému je opísaný v tejto habilitačnej práci (Cieľ 3). Údaje z NDS (moduly Chemical Occurrence Data a Ecotoxicology) boli použité pri zostavovaní puklikácie Ng a kol. (2023).

Kapitola 2

NORMAN Database System

Jedným z prínosov práce je vytvorenie databázového systému NORMAN (NDS – NORMAN Database System) ako referenčnej databázy, ktorá v jednej platforme zhromažďuje veľmi odlišné údaje z monitorovania chemických zlúčenín získané rôznymi technikami a v rôznych ekosystémoch, čím sa zabezpečí harmonizovaný prístup k zhromažďovaniu, ukladaniu, kontrole kvality, uchovávaniu a výmene údajov medzi členmi siete NORMAN. Vývoj systému sa riadi zásadami FAIR (Findable, Accessible, Interoperable, Reusable).

NDS spolupracuje s informačným systémom pre monitorovanie chemických zlúčenín (IPCHEM1) pri zhromažďovaní údajov o monitorovaní chemických cieľov a zároveň pripravuje pôdu pre rozvoj novej európskej infraštruktúry na spracovanie údajov pochádzajúcich z inovatívnych metód, ako je napríklad necieľový skríning (NTS – Non-Target Screening) a metódy založené na účinkoch (EBM – Effect-Based Methods).

Aktuálne NDS2 pozostáva z 13 modulov (obr. 2.1):

• Substance Database – databáza „emerging substances“,
• Suspect List Exchange – platforma na zdieľanie zoznamov zlúčenín potenciálne zodpovedných za vznikajúce riziká pre ekosystémy a ľudské zdravie,
• Chemical Occurrence Data – databáza, v ktorej sú uložené údaje monitorovania z rôznych zdrojov, zhromaždených v štandardnom formáte s cieľom uľahčiť porovnateľnosť a využívanie údajov v Európe a mimo nej,
• Ecotoxicology – databáza pre odvodenie noriem kvality životného prostredia,
• SARS-CoV-2 in sewage – databáza SARS-CoV-2 v odpadových vodách,
• Substance Factsheets – databáza súhrnných informácií o všetkých zlúčeninách zo Substance Database,

1Information Platform for Chemical Monitoring 2https://www.norman-network.com/nds/

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Obr. 2.1: Užívateľské rozhranie pre NORMAN Database System • Prioritisation – výsledky stanovenia priorít NORMAN zlúčenín, • Antibiotic Resistance Bacteria/Genes – databáza baktérií a génov rezistent-
ných voči antibiotikám, • Indoor Environment – databáza údajov vo vnútornom prostredí, • Bioassays Monitoring Data – databáza údajov získaných analýzou vzoriek
životného prostredia pomocou biologických testov, • Passive Sampling – databáza údajov získaných pomocou pasívnych vzorkovačov, • Digital Sample Freezing Platform – platforma digitálneho zmrazovania vzoriek
bola vytvorená na zdieľanie údajov hmotnostnej spektrometrie s vysokým rozlíšením, • MassBank Europe – databáza hmotnostných chromatogramov.

2.1. ARCHITEKTÚRA NDS

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2.1 Architektúra NDS

Tvorba architektúry databázového systému predstavuje zložitý proces, ktorý vyžaduje dôkladnú analýzu a plánovanie, aby sa zabezpečilo, že bude efektívne spĺňať potreby webovej aplikácie. Tento proces návrhu sme rozdelili do niekoľkých krokov.

Na začiatku projektu sme vykonávali analýzu s cieľom stanoviť, aké informácie budú zaznamenané a akým spôsobom bude systém ukladať a spracovávať tieto údaje. Našou hlavnou prioritou bola rýchlosť čítania a spracovania údajov, a to s ohľadom na obmedzenie hosťujúceho servera. V závislosti na metóde spracovania, analýzy a vizualizácie údajov sme vybrali dva rôzne spôsoby ukladania údajov (Tabuľka 2.1).

Moduly, ktoré sa nachádzajú v prvom riadku Tabuľky 2.1, majú veľký objem údajov. Dáta sú dobre štruktúrované a vzájomne prepojené. Pre takýto typ údajov je najvhodnejšie použiť databázu, ktorá umožňuje efektívne ukladanie, organizáciu a spracovanie údajov. Na prácu s databázou a tvorbu webových stránok s dynamickým obsahom sme použili programovací jazyk PHP, ktorý je jedným z najbežnejšie používaných programovacích jazykov pre vývoj webových aplikácií. Pre štatistické analýzy a výpočty sme zvolili jazyk R.

Jazyk R je použitý aj v moduloch z druhého riadku Tabuľky 2.1. Túto vetvu modulov vyvíja iná pracovná skupina v asociácii NORMAN. Moduly pracujú s väčším množstvom malých súborov.

Tabuľka 2.1: Spôsob uloženia údajov v moduloch

Modul	Substance Database	Chemical Occurrence Data	Ecotoxicology	SARS-CoV-2 in sewage	Substance Factsheets
Prioritisation	Antibiotic Resistance Bacteria/Genes				
Indoor Environment	Bioassays Monitoring Data				
MassBank Europe	Passive Sampling	Digital Sample Freezing Platform	Suspect List Exchange		
Typ úložiska	databáza	súbor			

2.1. ARCHITEKTÚRA NDS

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Pracovná skupina, ktorá vyvíja databázový systém, je tvorená zamestnancami Environmental Institute. Mojou úlohou je správa celého systému a vývoj 9 modulov (Substance Database, Chemical Occurrence Data, Ecotoxicology, SARS-CoV-2 in sewage, Substance Factsheets, Prioritisation, Antibiotic Resistance Bacteria/Genes, Indoor Environment, Bioassays Monitoring Data). Pri vývoji každého modulu aktívne spolupracujem s odborníkom z asociácie NORMAN, ktorý je expertom v príslušnej oblasti.
Vo zvyšnej časti práci sa budeme venovať iba modulom, ktoré priamo vyvíjame a spravujeme.
2.1.1 Návrh databázy
Navrhovanie databázového systému zahrňovalo niekoľko fáz. V prvej fáze sme vytvorili konceptuálny model databázy, ktorý opisuje entity (databázy, tabuľky), vzťahy medzi nimi a ich atribúty. Základná štruktúra databázy je reprezentovaná pomocou entitnorelačného diagramu (ERD), ktorý je zobrazený na Obr. 2.2. Tento obrázok reprezentuje iba pohľad na databázy, pretože celý systém obsahuje veľké množstvo tabuliek, ktoré nie je možné zobraziť. Ich počty sú uvedené v Tabuľke 2.2.
Empodat
SusDat
- Ecotox
Chemical Occurrence Data
Substance Database
Ecotoxicology
???
??
Factsheets
Substance Factsheets
←
Prioritisation
Prioritisation
Sars
SARS-CoV-2 in sewage
Bacteria
ARB&ARG
Indoor
Indoor Environment
Bioassay
Bioassays Monitoring Data
Obr. 2.2: ERD databázového systému NDS
Na základe konceptuálneho modelu sme vytvorili logický model databázy. Zadefinovali sme štruktúru tabuliek vrátane stĺpcov, primárnych a cudzích kľúčov a vzájomných vzťahov medzi nimi. V tejto fáze návrhu sme uplatnili normalizáciu s cieľom dosiahnuť 3. normálnu formu (3NF) pre tabuľky.
2.1. ARCHITEKTÚRA NDS
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Tabuľka 2.2: Počet tabuliek v jednotlivých databázach
Modul Substance Database Chemical Occurrence Data
Ecotoxicology SARS-CoV-2 in sewage Substance Factsheets
Prioritisation Antibiotic Resistance Bacteria/Genes (ARB&ARG)
Indoor Environment Bioassays Monitoring Data
Spolu
Databáza SusDat Empodat Ecotox Sars
Factsheets Prioritisation
Bacteria Indoor Bioassay
Počet tabuliek 26 109 42 1 25 4 42 46 42 337
Ako platformu na ukladanie dát sme sa rozhodli použiť relačný databázový systém MySQL. Fáza fyzického návrhu databázy pre MySQL zahrňovala definíciu tabuliek, kľúčov a obmedzení, indexáciu (pre zrýchlenie vyhľadávania), práva prístupu, zabezpečenie, atď.
2.1.2 Vkladanie údajov do databázy
Zhromažďovanie údajov o meraniach chemických zlúčenín si vyžaduje starostlivé plánovanie a pozornosť venovanú detailom, aby boli údaje správne zaznamenané a neskôr ľahko analyzovateľné. Z toho dôvodu bola vytvorená séria predpripravených súborov – DCT šablón (Data Collection Templates) v tabuľkovom procesore Microsoft Excel. Tieto dokumenty obsahujú určitú štruktúru a formátovanie, aby uľahčili vkladanie údajov. Štruktúra tabuliek vychádza z fyzického modelu databázy. Šablóny je možné získať zo stránky DCT Download, ktorá sa nachádza v každom module databázového systému.
Každý pracovný hárok pozostáva z textových buniek a z buniek s rozbaľovacími zoznamami. Rozbaľovacie zoznamy sú použité, pretože obmedzujú hodnoty, ktoré môžu byť zadané do bunky. Tým sa minimalizuje riziko chýb pri vstupe údajov a zabezpečuje sa konzistentnosť dát. Jednotlivé zoznamy na nachádzajú v samostatnom pracovnom hárku s názvom Drop-down lists.
Veľké súbory údajov, ktoré sú k dispozícii v inom formáte ako MS Excel, je možné nahrať po komunikácii s tímom NORMAN. V tomto prípade sa jedná o čisto ručné spracovanie údajov, pretože zvyčajne nie je dodržaný formát údajov. Sú to údaje priamo exportované z lokálnych databáz, najčastejšie vo formáte CSV alebo MS Access.
Asociácia NORMAN od začiatku vyvíja veľké úsilie na zabezpečenie toho, aby sa údaje zhromažďovali v štandardnom formáte s cieľom uľahčiť porovnateľnosť a využívanie
2.2. MODUL SUSPECT LIST EXCHANGE
8
údajov v celej Európe i mimo nej. Šablóny sú vypracované pre každý ekosystém a obsahujú informácie umožňujúce automatizované posúdenie kvality údajov (podrobnejšie detaily sú uvedené v našej práci Dulio a kol. (2020)).
2.2 Modul Suspect List Exchange

Suspect List Exchange3 (SLE) obsahuje 109 samostatných zbierok zoznamov podozrivých zlúčenín od viac ako 70 prispievateľov z celého sveta s celkovým počtom viac ako 100 000 jedinečných zlúčenín. Triedy zlúčenín zahŕňajú per- a polyfluóralkylové zlúčeniny, liečivá, pesticídy, prírodné toxíny, zlúčeniny s vysokým objemom výroby, na ktoré sa vzťahuje európske nariadenie REACH (ES: 1272/2008), prioritné kontaminanty vzbudzujúce obavy a regulačné zoznamy od partnerov asociácie NORMAN. Niekoľko zoznamov sa zameriava na produkty transformácie a komplexné prvky zistené v životnom prostredí s rôznymi úrovňami informácií o pôvode a štruktúre. Každý zoznam je k dispozícii na samostatné stiahnutie. Zlúčená zbierka je k dispozícii aj ako databáza zlúčenín NORMAN (Substance Database). Obsah SLE sa postupne integruje do veľkých otvorených chemických databáz, ako je PubChem4 a CompTox Chemicals Dashboard5, čo umožňuje ďalší prístup k týmto zoznamom spolu s ďalšími funkciami a vlastnosťami, ktoré tieto zdroje ponúkajú.

2.3 Modul Substance Database

Modul Substance Database6 (SusDat) predstavuje zoznam „emerging substances“. Je výsledkom zlúčenia všetkých zoznamov environmentálne relevantných zlúčenín pravidelne prispievaných partnermi NORMAN a aktivít spojených s NORMAN v rámci iniciatívy SLE. Pred konečnou integráciou do databázy zlúčenín SusDat sa systematicky spájajú a upravujú do vhodnej formy na import do databázy. Podrobnejšie je táto problematika vysvetlená v našej publikácii Taha a kol. (2022).

Od roku 2016 sa SusDat používa na prepojenie všetkých databáz NORMAN medzi sebou, ako aj NDS s hlavnými externými databázami.

2.4 Modul Chemical Occurrence Data

Modul Chemical Occurrence Data7 (Empodat) poskytuje prehľad referenčných hodnôt výskytu „emerging substances“ v celej Európe, ktoré sú zhromaždené v štandardnom

3https://www.norman-network.com/nds/SLE/ 4https://pubchem.ncbi.nlm.nih.gov/ 5https://comptox.epa.gov/dashboard/
6https://www.norman-network.com/nds/susdat/ 7https://www.norman-network.com/nds/empodat/

Tabuľka 2.3: Prehľad počtu záznamov v databáze Empodat

Ekosystém Vzduch Biota Sedimenty Kal z čističiek odpadových vôd Pôda Suspendované látky Voda

Percentuálny podiel 0,00 % 0,58 % 0,33 % 0,00 % 0,00 % 0,02 %

99,06 %

Počet údajov 147

559 875 311 794

2 837 358

22 548 94 823 196

9

formáte, aby sa uľahčila porovnateľnosť a využívanie údajov v celej Európe. V Empodat je k dispozícii viac ako 95 miliónov záznamov pre viac ako 4 500 zlúčenín (Tabuľka 2.3). Údaje pochádzajú najmä z vodného prostredia (sladká voda, odpadová voda, morská voda, podzemná voda, sediment a biota), ale vynakladá sa úsilie na zlepšenie pokrytia iných zložiek, najmä pôdy, ovzdušia a vnútorného prostredia.

Prostredníctvom modulu databázy Empodat združenie NORMAN nadviazalo spoluprácu s IPCHEM, oficiálnym európskym úložiskom monitorovacích údajov produkovaných národnými monitorovacími programami a výskumnými projektmi financovanými EÚ vo všetkých ekosystémoch. Na základe tejto spolupráce IPCHEMu pravidelne (na ročnej báze) poskytujeme údaje z databázy Empodat.

2.5 Modul Ecotoxicology

Modul Ecotoxicology8 (Ecotox) je určený na systematický zber a hodnotenie experimentálnych štúdií ekotoxicity, ako aj zostavenie existujúcich environmentálnych prahových hodnôt, ktoré sa tiež označujú ako „najnižšie“ predpovedané koncentrácie, ktoré nevykazujú toxicky účinok (Lowest PNEC). Takmer všetky zlúčeniny SusDat sa poskytujú s predpokladanými hodnotami PNEC9 a/alebo experimentálne založenými hodnotami účinku (ak sú k dispozícii) na výpočet rizík na podporu stanovenia priorít týchto zlúčenín.

V rámci tohto modulu sme tiež vyvinuli sériu online nástrojov:

PNEC Derivation – nástroj na odvodenie „cieľových hodnôt kvality“ (Quality Targets)

Search Quality Target – nástroj na výber jedinej spoločnej hodnoty PNEC (Lowest PNEC),

8https://www.norman-network.com/nds/ecotox/ 9PNEC – Predicted No-Effect Concentrations

10

Obr. 2.3: Formulár PNEC Derivation

CRED Evaluation – nástroj na identifikáciu spoľahlivých štúdií ekotoxicity na základe klasifikačného systému CRED.

Prístup k týmto nástrojom je obmedzený iba pre odborníkov asociácie NORMAN, ktorí sa špecializujúcu na ekotoxicitu.

PNEC Derivation

Nástroj PNEC Derivation (Obr. 2.3) umožňuje odvodiť Quality Targets z vybraných „spoľahlivých“ štúdií ekotoxicity. Základnou podmienku je, že musia byť zvolené minimálne tri štúdie. K dispozícii je formulár, v ktorom môžu odborníci prideľovať body 1, 2 a 3 jednotlivým štúdiám. Body 2 a 3 môžu byť priradené iba raz, pričom 3 bodmi by mala byť označená kľúčová štúdia. Na základe bodovania sa automaticky navrhnú metódy odvodenia PNEC a príslušný faktor hodnotenia AF. Hodnota PNEC je získaná ako podiel Effect value a AF. Aktívne odvodenia Quality Targets (riadky zo zeleným pozadím) vstupujú do nástroja Search Quality Target, v ktorom sa nachádzajú aj údaje z iných zdrojov (napr. portál REACH, databáza ETOX, predpovede QSAR, ...).

11

Obr. 2.4: Nástroj na hľadanie Lowest PNEC

Search Quality Target

Podobne, ako pri PNEC Derivation, aj v tomto prípade je k dispozícii formulár, v ktorom môžu odborníci prideľovať body 0, 1, 2 a 3 existujúcim Quality Targets. Body 1, 2 a 3 môžu byť priradené iba raz (1 – najnižšia priorita, 3 – najvyššia priorita). Na Obr. 2.4 je zobrazený formulár na voľbu Lowest PNEC pre zlúčeninu Triclosan. Hodnota PNEC, ktorá má v súčte najvyšší počet bodov (stĺpec Σ), sa stáva najmenšou hodnotou PNEC (Lowest PNEC). V druhej tabuľke na Obr. 2.4 môžeme vidieť ako sa menila hodnota Lowest PNEC pre zlúčeninu Triclosan. Na začiatku boli k dispozícii iba predbežné hodnoty PNEC (P-PNEC pred). Z nich si odborník PvO zvolil najmenšiu hodnotu (3/2018). Neskôr pribudli dve nové kolekcie hodnôt PNEC (10/2018 a 11/2022). Po každej kolekcii prebehla nová voľba Lowest PNEC. Aktuálna hodnota Lowest PNEC je v riadku so zeleným pozadím.

Zoznam hodnôt Lowest PNEC pre všetky zlúčeniny je voľne dostupný na stránke

2.5. MODUL ECOTOXICOLOGY
Tabuľka 2.4: Odvodenie hodnôt Lowest PNEC pre rôzne ekosystémy
Ekosystém Morská voda Sedimenty Biota (ryby) Morská biota (ryby) Biota (mäkkýše) Morská biota (mäkkýše)
Lowest PNEC Lowest PNECfw/10 Lowest PNECfw*2.6*(0.615 + 0.019*Koc) Lowest PNECfw*BCF Lowest PNECfw*BCF/10 Lowest PNECfw*BCF/4 Lowest PNECfw*BCF/10/4
12
Tabuľka 2.5: Priradenie kategórie na základe výsledku testu
Skóre > 75 % > 65 % > 35 % ≤ 35 %
Kategória 1 2 3 4
LOWEST PNECS10. Väčšina hodnôt Lowest PNEC je odvodená pre sladkú vodu (Lowest PNECfw). Pokiaľ neexistuje experimentálna hodnota, na odvodenie hodnôt Lowest PNEC sa používajú výpočty uvedené v Tabuľke 2.4, kde BCF je biokoncentračný faktor a Koc je koeficient adsorpcie v pôde. Parametre BCF a Koc sa nachádzajú v databáze Factsheets.
CRED Evaluation
Pri odvodzovaní PNEC je potrebné vyhodnotiť spoľahlivosť štúdií ekotoxicity. Nástroj CRED Evaluation (Obr. 2.5) využíva metódu hodnotenia CRED (Criteria for Reporting and Evaluating Ecotoxicity Data), ktorá zahŕňa 20 kritérií spoľahlivosti (Moermond a kol. (2016)).
Metóda hodnotenia CRED používa 4 kategórie spoľahlivosti: spoľahlivé (1 – reliable), spoľahlivé s obmedzeniami (2 – reliable with restrictions), nespoľahlivé (3 – not reliable) a nepriraditeľné (4 – not assignable). Podrobnejší opis týchto kategórií je uvedený v Moermond a kol. (2016). Podľa výsledkov testu sa štúdia zaradí do kategórie spoľahlivosti podľa Tabuľky 2.5.
10https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php
2.5. MODUL ECOTOXICOLOGY
13
Obr. 2.5: Formulár CRED Evaluation
2.6. MODUL SARS-COV-2 IN SEWAGE
14
Tabuľka 2.6: Prehľad počtu súborov údajov v databáze Sars podľa krajín.
Krajina Česká republika
Cyprus Fínsko Grécko Luxembursko Rakúsko Saudská Arábia Slovensko Španielsko Švédsko Taliansko
Počet súborov 23 91 9 758 2 59 12 87 119 10 18
2.6 Modul SARS-CoV-2 in Sewage
Od vypuknutia pandémie Covid19 skupiny zaoberajúce sa výskumom odpadových vôd na celom svete zbierajú vzorky odpadových vôd na testovanie prítomnosti vírusovej RNA SARS-CoV-2. Modul SARS-CoV-2 in sewage11 (Sars) je databáza, ktorá bola vytvorená na harmonizáciu metodík merania ľudských biomarkerov v odpadových vodách na hodnotenie životného štýlu, zdravia a expozície na úrovni komunity. Vznikla spoluprácou dvoch medzinárodných sietí NORMAN a SCORE12. Štruktúra databázy Sars umožňuje používateľom voľný prístup k údajom na úrovni ČOV, ako aj nahrávanie nových údajov prostredníctvom prispôsobenej šablóny na zber údajov (DCT), ktorá uľahčuje ich automatické nahrávanie do systému. Pri prístupe do databázy môžu používatelia vyhľadávať podľa krajiny a/alebo ČOV alebo si prezerať celý súbor údajov (v rámci databázy alebo ho možno exportovať do programu MS Excel) bez akýchkoľvek obmedzení. Údaje zobrazené na webovej stránke obsahujú dátum odberu vzoriek, kópiu génu (počet kópií/ml a/alebo ng RNA/ml), prahovú hodnotu cyklu
(Ct), názov ČOV a krajiny, obsluhovanú populáciu a počet osôb, ktoré boli v deň odberu vzoriek hlásené ako pozitívne na SARS-CoV-2 v spádovej oblasti kanalizácie. Detailnejšie informácie prinášame v publikácii Lundy a kol. (2021).
Databáza Sars k dnešnému dňu obsahuje 1188 súborov údajov z jedenástich rôznych krajín (Tabuľka 2.6).
11https://www.norman-network.com/nds/sars_cov_2 12https://score-cost.eu
Kapitola 3
Prioritizácia
Stanovenie priorít v oblasti chemických zlúčenín je jednou z úloh pre odborníkov na ochranu životného prostredia a úradov s rozhodovacími právomocami, a to z hľadiska
• definovania prioritných opatrení na prevenciu a kontrolu znečistenia,
• prideľovania zdrojov na riešenie existujúcich nedostatkov v poznatkoch nákladovo efektívnym spôsobom.
V tejto súvislosti by sa údaje z monitorovania chemických zlúčenín mohli systematickejšie a efektívnejšie využívať na účely množstva právnych predpisov EÚ týkajúcich sa chemických zlúčenín. V prípade veľkej väčšiny zlúčenín prítomných alebo predpokladaných v životnom prostredí však väčšina údajov potrebných na podporu rozhodovacieho procesu chýba alebo má nízku kvalitu. Nedostatočné údaje sú jednou z hlavných príčin nedostatočne účinných opatrení na reguláciu kontaminantov vzbudzujúcich obavy (Dulio a kol. (2020)). Nedostatok poznatkov o expozícii ľudí a životného prostredia chemickým látkam uznáva Komisia a členské štáty vo viacerých politických dokumentoch a opatreniach (Carusi a kol. (2022)). Európska komisia prijala v októbri 2020 stratégiu EÚ pre udržateľnosť chemických zlúčenín smerom k životnému prostrediu bez toxických zlúčenín (European Commission: Chemicals Strategy for Sustainability Towards a Toxic-Free Environment, 2020) ako súčasť implementácie „Zelenej dohody“. Navrhuje sa v nej jasný plán a časový
harmonogram na riešenie súčasných nedostatkov v znalostiach a účinnejšie a efektívnejšie fungovanie právnych predpisov o chemických zlúčeninách v záujme bezpečného a udržateľného používania chemických zlúčenín. Jedna z obzvlášť dôležitých oblastí súvisí s inovatívnym využívaním údajov z monitorovania chemických zlúčenín a údajov o nebezpečenstve, aby sa rozhodovacím orgánom poskytlo viacero dôkazov na identifikáciu skupín chemických zlúčenín, koncových bodov a zdrojov, ktoré sa musia prioritne riešiť.
Do modulu s názvom Prioritisation sme integrovali aplikáciu Customized Statistics. Vývoj aplikácie bol postavený na publikáciách Dulio a Slobodnik (2015); Dulio a von der Ohe (2013); von der Ohe a kol. (2011). Tento modul poskytuje odborníkom
15
16
na ochranu životného prostredia prehľad o stave poznatkov a medzier v poznatkoch pre správne posúdenie rizika znečisťujúcich zlúčenín vzbudzujúcich obavy v životnom prostredí.

Pôvodne sme aplikáciu Customized Statistics vytvorili v programovacom jazyku PHP s cieľom zabezpečiť istú kompatibilitu s NDS. Neskôr sme zistili, že má veľké obmedzenie v porovnaní s pokročilejšími nástrojmi na analýzu dát, najmä pokiaľ sa pracuje s veľkými a zložitými súbormi dát. V takýchto prípadoch je vhodné zvážiť použitie špecializovaných nástrojov na analýzu a správu dát, ako je napríklad Python alebo jazyk R s knižnicami na analýzu dát. Aby sme zabezpečili kompatibilitu s inými vyvíjanými modulmi NDS (Passive Sampling a Digital Sample Freezing Platform), rozhodli sme sa pre jazyk R.
Výstupy z našej vedeckej práce boli rozpracované aj na študentskej úrovni. V diplomovej práci (Nosko, 2019) sme implementáciu aplikácie Customized Statistics previedli z jazyka PHP do jazyka R. Aplikácia prechádza pravidelne testovaním a pridávaním nových funkcionalít na zabezpečenie efektívnosti spracovania údajov a užívateľského komfortu.
Koncepcia prioritizácie zahŕňa dvojstupňový prístup, v ktorom sa látky najprv zaradia do hlavných kategórií opatrení na základe zistených nedostatkov v poznatkoch a opatrení potrebných na ich riešenie. Priorita v rámci každej kategórie sa potom hodnotí na základe špecifického výskytu, nebezpečnosti (perzistencia, bioakumulácia, mobilita, potenciál endokrinných porúch atď.) a ukazovateľov rizika, ako sú frekvencia prekročenia (FoE) a rozsah prekročenia (EoE) najnižších hodnôt PNEC (Lowest PNEC) (Dulio a kol. (2020)).
Experti z asociácie NORMAN identifikovali šesť hlavných kategórií na základe najčastejšie identifikovaných nedostatkov v poznatkoch (Dulio a von der Ohe (2013) – Tabuľka 3.1):
Aplikácia Customized Statistics kategorizuje jednotlivé zlúčeniny na základe vývojového diagramu na Obr. 3.1. Užívatelia môžu prostredníctvom formulára na Obr. 3.2 zadať vstupné údaje do procesu kategorizácie. Aplikácia využíva údaje získané automaticky z NDS, vrátane kandidátskych zlúčenín na stanovenie priorít (databáza SuSdat), georeferenčných údajov z monitorovania zlúčenín (databáza Empodat), údajov o ekotoxikologických účinkoch (databáza Ecotox), fyzikálno-chemických a iných vlastností záujmových zlúčenín (databáza Factsheets). Výsledkom celého procesu je rozsiahla tabuľka na Obr. 3.3. Kvôli lepšiemu zobrazeniu bola rozdelená do 4 riadkov. Zobrazenie tabuľky sa da rozšíriť o ďalších 36 stĺpcov s pomocnými údajmi.
Je dôležité zdôrazniť, že proces kategorizácie**[2520»]**zlúčenín a určovania priorít je iteračný proces, ktorý zahŕňa pravidelnú revíziu prioritných zlúčenín v každej kategórii vždy, keď sa získajú nové informácie a/alebo spoľahlivejšie údaje alebo keď je k dispozícii spätná väzba z uplatňovaných opatrení na zníženie emisií (Dulio a von der Ohe (2013)).
17
Tabuľka 3.1:**[«2520]**Zoznam kategórií prioritných opatrení
Kat.
Súčasná situácia / medzery v poznatkoch
Kategórie opatrení / činnosti potrebné na riešenie nedostatkov v poznatkoch
Dostatočné dôkazy o vystavení a Požadované kontrolné a zmierňujúce opat-
1
prekročení spoľahlivých prahových renia / začlenenie do bežného monitorovahodnôt, ktoré nie sú nebezpečné nia a odvodenie právne záväzných noriem
(normy kvality)
kvality
Hodnotenie nebezpečnosti je za- Pozorovací zoznam: skríningové štúdie po-
2
ložené na experimentálnych úda- trebné na získanie informácií o súčasných joch, ale na malom množstve úda- úrovniach vystavenia a priestorovom roz-
jov z monitorovania
ložení
3
Dôkaz o expozícii, ale hodnotenie nebezpečnosti je založené na predpokladaných údajoch o (eko)toxicite (P-PNEC)
Pred prijatím konečného záveru o riziku je potrebné spoľahlivé posúdenie nebezpečenstva
4
Analytické možnosti zatiaľ nie sú uspokojivé
Hodnotenie nebezpečenstva je založené na experimentálnych údajoch, ale analytické výsledky ešte nie sú uspokojivé
Žiadne alebo len málo údajov z mo-
5
nitorovania a hodnotenie nebezpečnosti je založené na predpokladaných údajoch o (eko)toxicite (P-
Potrebné sú skríningové štúdie a spoľahlivé hodnotenie nebezpečenstva
PNEC)
Dostatočné dôkazy o expozícii a neprekročení spoľahlivých prahových Monitorovanie týchto zlúčenín by sa 6 hodnôt, ktoré nie sú nebezpečné mohlo znížiť, ale mali by sa kontrolovať (normy kvality) a ktoré sú vyššie riziká zmesi pre často zistené zlúčeniny ako analytická LOQ
18
List of emerging substances
?
Is the substance sufficiently investigated and are there sufficient quantified data in the relevant matrix(ces)?
??
?
Substance insuffiently (or never) Substance sufficiently monitored Substance sufficiently monitored
monitored
but low frequency of quantification and quantified in relevant matrix
Sufficient
experimental toxicity
data for hazard
yes
assesment?

?
Sufficient analytical performance?
>100 sites with LOQ < PNEC? no
??
LOQ (best performance) < PNEC?
?
yes Sufficient experimental
- toxicity data for
hazard assesment?
yes
?
Cat. 2
Watch list ⇒ investigate occuurence
no
?
Cat. 5
Improve (eco)toxicological data and
monitoring
no
?
Cat. 4
Improve analytical performance
yes
?
Risk of exceedance of the lowest PNEC?
yes no
?
Cat. 1
?
Cat. 6A Cat. 6B
Regulatory monitoring Potential Low
large scale (1A);
mixture priority
local scale (1B)
risk
no
?
Cat. 3
Improve (eco)toxicological data
‘ Novel endpoints 6
Obr. 3.1: Pracovný postup NORMAN na kategorizáciu nových zlúčenín (Dulio a von der Ohe (2013))
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Obr. 3.2: Customized Statistics – formulár Obr. 3.3: Customized Statistics – výsledok
Kapitola 4
Záver
Predložená práca sa sústreďuje na metodiku návrhu, tvorbu a implementáciu databázového systému, ktorý obsahuje rozsiahle informácie o chemických zlúčeninách, ktoré predstavujú riziko pre životné prostredie a ekosystémy. Toto automatizované databázové riešenie je základom pre budúce inovatívne aplikácie na posudzovanie potenciálnych rizík a nebezpečenstva spojeného s týmito zlúčeninami v životnom prostredí.
Aktuálne databázový systém poskytuje nástroje na usmernenie expertov pri:
• identifikácii spoľahlivých štúdií ekotoxicity na základe klasifikačného systému CRED (Moermond a kol. (2016)),
• výbere jedinej spoločnej hodnoty PNEC (Lowest PNEC) dohodnutej ako výsledok celoeurópskych konzultácií expertov.
Do databázového systému sme integrovali aplikáciu, ktorá poskytuje odborníkom na ochranu životného prostredia prehľad o stave poznatkov a medzier v poznatkoch pre správne posúdenie rizika znečisťujúcich zlúčenín vzbudzujúcich obavy v životnom prostredí.
Budúci rozvoj databázového systému by sa mal zamerať na: • vytvorenie univerzálneho API rozhrania na lepšiu výmenu informácií (v súčas- nosti existujú iba rozhrania API, ktoré boli prispôsobené potrebám niekoľkých konkrétnych organizácií), • nasadenie umelej inteligencie (napr. formou strojového učenia) na spracovanie, vyhľadávanie a verifikáciu obrovského množstva údajov o chemických zlúčeninách z rôznych zdrojov.
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C O M M E N TA R Y
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The NORMAN Association and the European Partnership for Chemicals Risk Assessment (PARC): let's cooperate!
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Heinz Ruedel44, Saer Samanipour45, Tobias Schulze14, Emma L. Schymanski46, Manfred Sengl47, Peter Tarábek35, Dorien Ten Hulscher48, Nikolaos Thomaidis11, Anne Togola33, Sara Valsecchi41, Stefan van Leeuwen4, Peter von der Ohe2, Katrin Vorkamp49, Branislav Vrana28 and Jaroslav Slobodnik8*†
Abstract
The Partnership for Chemicals Risk Assessment (PARC) is currently under development as a joint research and innova□ tion programme to strengthen the scientific basis for chemical risk assessment in the EU. The plan is to bring chemi□ cal risk assessors and managers together with scientists to accelerate method development and the production of necessary data and knowledge, and to facilitate the transition to next-generation evidence-based risk assessment, a non-toxic environment and the European Green Deal. The NORMAN Network is an independent, well-established and competent network of more than 80 organisations in the field of emerging substances and has enormous potential to contribute to the implementation of the PARC partnership. NORMAN stands ready to provide expert advice to PARC, drawing on its long experience in the development, harmonisation and testing of advanced tools in relation to chemicals of emerging concern and in support of a European Early Warning System to unravel the risks of contami□ nants
of emerging concern (CECs) and close the gap between research and innovation and regulatory processes. In this commentary we highlight the tools developed by NORMAN that we consider most relevant to supporting the
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PARC initiative: (i) joint data space and cutting-edge research tools for risk assessment of contaminants of emerging concern; (ii) collaborative European framework to improve data quality and comparability; (iii) advanced data analysis tools for a European early warning system and (iv) support to national and European chemical risk assessment thanks to harnessing, combining and sharing evidence and expertise on CECs. By combining the extensive knowledge and experience of the NORMAN network with the financial and policy-related strengths of the PARC initiative, a large step towards the goal of a non-toxic environment can be taken.
Keywords: NORMAN network, Suspect screening, Non-target screening, Contaminants of emerging concern, Environmental monitoring, High-resolution mass spectrometry, Effect-based methods, Chemical risk assessment and prioritisation

Background The PARC partnership is currently under development as a joint research and innovation programme to support the European Commission (EC) and national chemical risk assessment and management authorities by providing new evidence and methodologies and promoting their uptake in regulatory processes. This applies to currently recognised as well as potential future contaminants of emerging concern (CECs).

Over the past 15 years, the NORMAN Association has developed a network of expert organisations in the field of CECs in the environment. This effort fits well with the aims and structure of the PARC initiative [1] for a European Partnership for Chemicals Risk Assessment. It is therefore no surprise that NORMAN fully supports the “evolution, not revolution” principle of the PARC initiative, and agrees that existing data and methods should be integrated and further developed without “reinventing the wheel”, as we explain in more detail in this paper.

In the PARC partnership, the plan is to join forces with scientists to create the next generation of chemical risk assessment and to facilitate ‘The European Green Deal’ [2], which includes the sustainable management of chemicals for a non-toxic environment. An essential role of this partnership is to foster better use of existing knowledge and data, and better cooperation and coordination of research on the regulatory needs—all in order to improve risk assessment and management, including the development of an EU early warning system for emerging risks of chemicals in the environment.

The European Commission acknowledges the importance of continuously improving knowledge about the (eco)toxicity of chemicals and of adequately addressing uncertainties regarding exposure to chemicals [3, 4]. Moreover, current regulations are not sufficiently effective to tackle CECs and chemical risks in general, since a holistic view is missing and there are often inconsistencies between different use sectors [5]. The vision for future chemicals policy is that chemicals should be dealt with in an integrated manner in an overarching
chemicals policy framework covering all types of chemicals and all uses, beyond the current sector-specific regulations.

It is in this context that the NORMAN network came into existence in 2005 as a project, following a call by the EC (DG Research) aimed at creating a permanent platform to reduce knowledge gaps and better meet the requirements of risk assessors and risk managers concerning CECs [6]. NORMAN is today an independent, self-funded, non-profit, multidisciplinary and multinational association in the field of CECs in the environment, which brings together more than 80 organisations representing various stakeholders, including competent authorities, national reference laboratories, research centres, academia and industry—mostly in Europe, but also in North America and Asia [7].

The missions of NORMAN are to: (i) facilitate a more rapid and wider exchange of data on the identity, occurrence and effects of CECs in water, biota, air, soil and indoor environment; (ii) improve data quality and comparability via validation and harmonisation of common sampling and measurement methods (chemical and biological), and (iii) provide tools for the risk and hazard assessment of CECs [6]. Since the primary objective of the NORMAN Association is to act as a science-topolicy interface, the outcomes of the network’s activities are regularly shared with the EC’s services including DG Environment, European Chemicals Agency (ECHA), European Environment Agency (EEA), EC Joint Research Centre (JRC), international river commissions, regional sea conventions and national regulatory bodies. Currently, nine national regulatory agencies are members of the NORMAN Association.

The NORMAN Association has considerable—and continuously developing—experience of establishing: (i) a consolidated network of closely cooperating laboratories active in research to support chemical risk assessment and management; (ii) a joint, user-friendly and openaccess data space to share knowledge on CECs in the environment and promote harmonised protocols for data collection and reporting; (iii) a collaborative framework

to foster validation and harmonisation of measurement methods and monitoring tools; (iv) advanced data analysis tools to deal with less-investigated substances in support of a European early warning system to detect emerging chemical risks to the environment, and (v) a system for harnessing, combining and sharing expertise among research teams, national reference laboratories and environmental agencies in innovative methods in support of chemical risk assessment. So far, NORMAN has been strongly involved in CECs in the fresh water aquatic environment and the associated EU policies. The focus has recently extended beyond fresh water to the indoor, marine, soil and terrestrial environments and water reuse, while the scope of CECs is also expanding to include additional parameters such as antibiotic resistance determinants and microplastics.

In this opinion paper we would like to highlight the tools developed by NORMAN that we consider most relevant to support the PARC initiative. Joint data space and cutting□edge research tools for risk assessment of contaminants of emerging concern NORMAN Database System (NDS): data gathering and data management Perspective and recommendations Continue to develop the NORMAN Database System (NDS) as a reference database that brings together, in a single platform, widely differing chemical monitoring data acquired using various techniques and in different matrices, thereby ensuring a harmonised approach for data collection, storage, quality control, curation and exchange among NORMAN members and more widely. Future platform development will be guided by the FAIR principles (Findability, Accessibility, Interoperability, and Reuse of data).

The NDS is complementary to the EC Information Platform for Chemical Monitoring (IPCHEM) [8, 9] in harvesting chemical target monitoring data, while at the same time paving the way for the development of a new European infrastructure for handling data coming from innovative methods, such as non-target screening (NTS) and effect-based methods (EBM). It should continue in that role.

Rationale The crucial task of gathering and managing environmental CEC exposure data to support chemical risk assessment has been the core activity of the NORMAN Association from its start in 2005.

The current NDS [10] is an open-access platform of interconnected databases able to assist effective and
rapid screening and risk assessment of contaminants in the environment.

The unique feature of the NDS is that it provides a comprehensive set of data on CECs together with a range of innovative applications for their hazard and risk assessment. These tools range from physico-chemical properties, use characteristics, mass spectral information, and exposure data from target and non-target screening in all environmental compartments, to ecotoxicity data and in situ bioassay signals reflecting mixture toxicity. The NDS currently consists of 12 modules (Fig. 1), of which eleven (Substance Database (SusDat); Suspect List Exchange (SLE); Chemical Occurrence Data (EMPODAT); Ecotoxicology; Bioassays Monitoring Data; MassBank Europe; Digital Sample Freezing Platform (DSFP); Indoor Environment; Passive Sampling; Substance Factsheets; Prioritisation) are accessible, interlinked and populated with data. The 12th is an antibiotic-resistant bacteria and genes module (ARB&ARG) that is still under development, while a new module hosting data on microplastics is currently being designed.

A selection of the NDS modules most relevant to PARC is presented below.

NORMAN Substance Database: a common list of substances for harmonised chemical risk assessment Perspectives and recommendations Further develop the Substance Database (SusDat) as the cornerstone of a common European platform where information on highly relevant and newly discovered environmental pollutants can be shared in a harmonised format [11].
Rationale A common, harmonised list of chemical compounds shared among all parties in research and regulation is one critical requirement for enhanced cooperation among existing regulatory frameworks and shifting towards a “one chemical, one assessment” paradigm. However, current chemicals lists are fragmented collections, with researchers and regulators all using their own lists.
We believe that the combination of NORMAN Suspect List Exchange (SLE) [12] and the merged NORMAN Substances Database [13] of the NDS could be a globally leading model for collaboratively working towards such a list. Numerous organisations, national and international regulatory agencies and research groups from Europe and North America already contribute to this initiative. NORMAN SLE is a platform to share lists of substances potentially responsible for emerging risks to ecosystems and human health. The submitted lists are shared with US EPA CompTox Chemicals Dashboard [14, 15] and PubChem [16, 17] and are published on Zenodo [18]. By
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Fig. 1 The NORMAN Database System (NDS)
acting as a data collector, the NORMAN SLE has become an important source of specialised research information for major chemical databases such as PubChem and CompTox, beyond the realms and means of individual researchers. In return, the integration of the NORMAN SLE into major chemical databases adds enormous value to the original contributions, offering up new functionality for all parties.
The merged list (without duplicates) is known as NORMAN SusDat [13]—a curated compound database (65,697 compounds as of April 2020), where substances are merged by the Standard InChIKey, which acts as the unique identifier. This is accompanied by other structural information such as CAS numbers and SMILES, as well as physico-chemical properties. SusDat also contains mappings to the equivalent “MS Ready” forms [19], as well as other mass spectrometric information for the identification of compounds with NTS techniques, estimated (in silico) Predicted No-Effect Concentrations (PNECs), and other information required for the
prioritisation and risk assessment of substances. Since 2016, SusDat has been used to interlink all NORMAN databases among themselves, as well as the NDS with major external databases.
NORMAN Ecotoxicology Database: a common platform for ecotoxicity assessment Perspectives and recommendations Establish a core team of ecotoxicology experts, from EU Member States and globally, using the Ecotoxicology Database as a basis to evaluate the reliability and relevance of ecotoxicity studies and reach consensus on Quality Standards (i.e. PNEC values) for a more harmonised risk assessment of chemicals.
Rationale We propose to share the NORMAN Ecotoxicology Database [20] for harmonised ecotoxicity assessment within the PARC partnership. The database provides a transparent tool to guide experts in: (i) the identification of the
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reliable ecotoxicity studies, based on the CRED (Criteria for Reporting and Evaluating ecotoxicity Data) classification system [21]; (ii) the online derivation of a set of quality standards for each matrix and regulatory framework based on selected ‘reliable’ ecotoxicity studies, using a built-in software tool implementing the requirements of the EC guidelines [22], and (iii) the final selection of a single, common PNEC value, agreed upon as a result of Europe-wide expert consultations.
At present the database comprises, for almost all SusDat substances (i.e. > 65,000), at least one in silico PNEC [23] based on predicted acute effects for each of the three basic trophic levels of the fresh water compartment (fish, daphnia, and algae), which are used when experimental toxicity data are insufficient or not available. In 2019, a semi-automated tool for retrieving experimental (eco) toxicity data from the US EPA ECOTOX Knowledgebase allowed the import of > 125,000 experimental data on standard (eco)toxicity endpoints for about 5000 SusDat substances in a format compatible with the metadata requirements of the NORMAN Ecotoxicology Database. Additional experimental (eco)toxicity data and threshold values will be retrieved from other databases such as the REACH portal, the ETOX database of the German Federal Environment Agency, as well as existing PNECs and Quality Standards (EQS) from various regulatory sources. The (eco)toxicity threshold values used for chemicals prioritisation are agreed by experts
and referred to as ‘Lowest PNECs’. These values are generally calculated for the fresh water matrix and then converted to an equivalent PNEC value for marine water, sediment and biota matrices (for example, bioconcentration factors (BCF) are used for conversion to equivalent PNECs for biota).
EMPODAT: a database of target monitoring data Perspectives and recommendations Provide a Europe-wide standard for essential quality information (metadata) accompanying chemical analysis results and commonly agreed minimum requirements to allow interoperability of archived monitoring data.
Rationale A game changer for next generation chemical risk assessment is a system able to provide comprehensive information on the exposure of humans and the environment to large numbers of chemicals during the entire life cycle of products, including waste and recycled products. With the EMPODAT database module [24] of the NDS, the NORMAN Association has already established a collaboration with IPCHEM, the official European repository of monitoring data produced by national monitoring programmes and EU-funded research projects in all matrices and compartments. EMPODAT today
hosts approximately 10.3 million geo-referenced target monitoring data of more than 3100 substances in water (surface, ground, and waste water), sediment, biota, soil, sewage sludge and air matrices. The data are publicly accessible and provide an overview of benchmark values on the occurrence of contaminants of emerging concern across Europe. From the start, NORMAN has made a great effort to ensure that the data are gathered in a standard format in order to facilitate data comparability and exploitation across Europe and beyond. These spreadsheet-based Data Collection Templates (DCTs) were developed for each of the matrices, and contain information allowing for automated assessment of data quality.
Non-target screening (NTS) tools and Digital Sample Freezing Platform (DSFP) for retrospective suspect screening of environmental contaminants Perspectives and recommendations Establish a federated European infrastructure storing raw non-target screening data converted into a common (open) format, designed for retrospective screening.
Establish a central platform/database storing regularly updated information on available data sets Europe-wide and, eventually, at a global scale. Apply commonly agreed workflow(s) for retrospective analysis to identify and prioritise pollutants frequently detected in environmental samples.

Rationale Thanks to NTS techniques it is possible to obtain an overview of human and environmental exposure to thousands of chemicals simultaneously, with a high level of sensitivity and selectivity, including chemicals that have not been identified previously [25]. The NTS workflows (comprising wide-scope target, suspect and non-target screening) based on full scan, high-resolution mass spectrometry (HRMS), developed by NORMAN members, represent the state-of-the-art methods to deal with realworld contaminant mixtures in a more holistic way. Active since 2013, the NORMAN NTS Working Group has built a strong collaborative infrastructure and developed innovative tools to facilitate exploitation and interpretation of complex data produced by full scan, HRMS methods. NORMAN members have also developed protocols to implement NTS in routine, regulatory applications. Suspect screening of pre-defined lists of tens to tens-of-thousands of known substances in each sample (supported by NORMAN SLE and NORMAN SusDat) is presently the recommended way forward.
In this context the Digital Sample Freezing Platform [26] is a key tool developed by NORMAN to support suspect and non-target screening. This novel technology

allows the storage of thousands of high-resolution mass spectra (fingerprints) of all chemicals, metabolites and transformation products detected in each of the analysed samples. Thanks to this platform, it is possible for users to search retrospectively for a large number of compounds (e.g. those in SusDat; see above) in all the “digitally frozen” samples stored in the database and obtain reliable qualitative and semi-quantitative data on their occurrence in the investigated samples.
Further key tools, supported by NORMAN and embedded in the NDS, to assist non-target screening, are:
- MassBank Europe, an open-source, open-access database of mass spectra to support higher confidence identification of suspects and non-targets [27, 28]. Based on MassBank Japan, MassBank Europe was founded in 2011, arising from a NORMAN initiative. Today MassBank contains over 80,000 unique mass spectra for > 14,300 compounds (database release 2020.05 [29]), including mass spectra of tentatively identified compounds. MassBank Europe is a core service for NORMAN as well as for other initiatives such as HBM4EU (Human Biomonitoring for Europe) initiative [30], ELIXIR [31], the German Network for Bioinformatics Infrastructure (de. NBI) [32] and the German National Research Data Infrastructure Initiative for Chemistry (NFDI4Chem) [33];
- A Retention Time Index (RTI) prediction model [34, 35] allowing for tentative identification of each compound in SusDat as a combination of its exact mass, MS/MS fragments and the predicted RTI value, reduces the number of false positives in suspect screening.

Thanks to all the above-mentioned interconnected tools, DSFP can provide reliable qualitative and semiquantitative data on the occurrence of already identified as well as novel CECs, thereby providing exhaustive insight into the spatial and temporal distribution of contaminant mixtures in the environment, making NORMAN DSFP a virtual environmental observatory on chemical contamination. Extensions of DSFP for additional chemicals captured in SusDat (e.g. highly polar molecules and gas chromatography-only amenable substances) are under way.
Collaborative European framework to improve data quality and comparability: development and harmonisation of methods Perspectives and recommendations Build the capacity of laboratories in Europe and globally by systematic organisation of international Collaborative Trials addressing analysis of CECs in various matrices by novel analytical technologies.
Pursue progressive testing and implementation of novel sampling and analytical methodologies to help design smart(er) monitoring strategies that can be applied in regulatory monitoring activities.
Rationale NORMAN brings together the leading European institutions in the development and harmonisation of measurement methods for the detection of emerging chemicals in the environment. The studies organised by the network represent a crucial step for the scientific community and for environmental agencies for validation and harmonisation of innovative sampling and monitoring tools before their possible future implementation in regulations.
NORMAN is the author of the first common framework for validation of chemical and biological monitoring methods—a protocol which is now adopted as a Technical Specification (TS) of the European Committee for Standardization (CEN) (CEN TS 16800:2015) [36, 37].
More than 15 collaborative trials have been organised by NORMAN since 2006 on a wide range of methods, including non-target screening in water [38], sediment [39], indoor dust [40] and biota [41], in vitro and in vivo bioassays [42] and passive sampling [43, 44]. They have tackled aspects relevant to monitoring and early warning of CECs in the environment and approaches to hazard assessment, including integration of effect-based methods with chemical analysis to improve interpretation of cause–effect links. These trials included not only the assessment of sample preparation and instrumental performance, but also the evaluation of the impact that computational and data processing tools have on interpretation of results.
Advanced data analysis tools: towards a European Early Warning System Prioritisation of substances and priority setting Perspectives and recommendations Systematically collect wide-scope target, suspect and non-target screening data at European scale to improve the spatial and temporal coverage and range of matrices available for risk assessment.
Identify compounds for which robust (eco)toxicity studies are needed as a priority.
Prioritise chemicals for which standards or mass spectra will be required from industry, to enable their detection in the environment.
Develop dynamic open-access links to spatially detailed information about production, uses, exposure to and consumption of chemicals.

Develop a common European scheme for grouping of chemicals and indicator substances, based on various criteria including sector of use, chemical structure and mode of action.
Integrate more strongly chemical analytical and effectbased methods in order to identify effect and (mixture-) risk drivers, i.e. substances or groups of substances that should be selected for further risk assessment.
Rationale In the past decade, NORMAN has developed an integrated strategy to deal with less-investigated substances for which knowledge gaps are identified (e.g. insufficient information on the exposure levels and/or adverse effects, or inadequate performance of the analytical methods for their measurement in the environment) [45]. The concept involves the application of a decision tree which allows the allocation of substances into six main action categories, based on the identified knowledge gaps and actions needed to address them. The priority within each category is then evaluated on the basis of specific occurrence, hazard (persistence, bioaccumulation, mobility, endocrine disruption potential, etc.) and risk indicators such as the Frequency of Exceedance (FoE) and Extent of Exceedance (EoE) of the Lowest PNECs.

Various aspects of a categorisation/ranking system have been scaled up and tested in numerous large-scale European projects and national prioritisation processes such as defining Water Framework Directive (WFD) River Basin Specific Pollutants (RBSP) in the Danube River Basin [46] or selecting national Watch List substances and RBSP in France [47, 48] and in The Netherlands [49]. In this way, NORMAN aims to provide a scheme for harmonised RBSP assessment across the EU. On a regular basis, NORMAN also makes recommendations to the Commission regarding substances to be added to the list of WFD Priority Substances and EU Watch List [50].
This workflow, originally designed to work with target monitoring data, now integrates the automatic query of NTS mass spectral information archived in DSFP (see above). Thanks to DSFP and the set of fully integrated tools and databases developed by NORMAN, it is now possible to obtain an overview of the state of knowledge (spatial distribution of contaminants, degree of exceedance of threshold values based on semi-quantified data, etc.) of a dynamically updated list of > 60,000 chemicals, including many never studied before, and to identify priority substances/groups of substances for which further actions need to be taken.
This approach fits well with the requirements of an Early Warning System, where the data to correctly identify an emerging risk at an early stage are typically limited or of poor quality. In this context, it is important to use
a transparent and rational approach for signal identification and characterisation that is able to deal with the knowledge gaps that still prevent proper risk assessment and risk ranking of most emerging substances. Individual components of the Early Warning System concept, such as NormaNEWS, have already been trialled [51].
Effect□based methods (EBM) for monitoring of chemical mixtures in the environment Perspectives and recommendations Systematically include NTS and EBM in investigative monitoring programmes to support chemicals risk assessment.
Further develop and implement effect-based methods in a wider range of environmental compartments, including the marine and terrestrial environments.
Harmonise, and provide training on, the use of effectbased methods.
Rationale Bioassays are the only currently available methods able to respond to the recently recognised need to address unknown mixture risks present in the environment, which can then be linked to specific chemical compounds via chemical analysis [52, 53].
NORMAN is actively contributing to the construction of a common position of the European experts on the use of bioassays in the regulatory framework of the WFD, in particular with the definition of a battery of bioassays for chemical water quality assessment [54]. Besides an interlaboratory study organised in 2009 to assess the comparability of results obtained with a battery of bioassays [42] and a comprehensive literature review on the development of an ecotoxicological perspective on neurotoxicity assessment [55], NORMAN contributed to the Science to Policy Interface (SPI) Estrogen monitoring project (a voluntary initiative of 12 countries and 24 organisations in Europe), which has recently provided concrete demonstration data about the performance of the tested EBM [56].
In terms of practical implementation of EBMs in the regulation, another crucial step is the determination of effect-based trigger values (EBT), which define the acceptable level of effect for each toxicological endpoint of concern and thus allow environmental managers to interpret EBM data and distinguish between more and less polluted sites. In collaboration with the SOLUTIONS project (FP7/603437), NORMAN has contributed to the drafting of a proposal for a harmonised methodology for the definition of effect-based trigger (EBT) values [57] and the way to proceed when an EBT is exceeded [58, 59].

In contrast to EQSs, EBTs consider all chemicals in a mixture contributing to a measured effect in a given sample. Explaining the observed activity detected by the applied bioassays and addressing the combined effect of chemicals can be done (using mass balances/'iceberg modelling') by calculation of Toxic Units (TU) for each of the quantified pollutants or Bioanalytical Equivalent concentrations (BEQ), depending on the bioassay. This should be followed by a comparison of the estimated ∑TU or BEQ from the component-based assessment with the TU and BEQ derived from the bioassay testing. If EBTs are exceeded and the component-based assessment cannot explain the activity detected in the bioassay, an Effect-Directed Analysis (EDA) protocol should be performed in order to identify the risk drivers [54, 60, 61].
In this context, NTS-based approaches are key to improving the identification of risk drivers and facilitating compound/mixture prioritisation in different matrices. As a matter of fact, large datasets from non-target screening and effect-based methods can be explored using multivariate statistics and pattern recognition methods to identify peaks that co-vary with detected effects (virtual effect-directed analysis). The NORMAN Joint Programme of Activities promotes this type of study as a way to identify candidate compounds for further investigation [41].
Finally, as part of its latest Joint Programme of Activities, NORMAN will develop a bioactivity database. This project aims to support the interpretation of effect-based monitoring data for mixture toxicity modelling. A richer set of bioactivity data will be crucial to understanding the contribution of detected chemicals to the observed effect in the different assays. Currently, the lack of effect data for the detected chemicals in different assays is a major limitation and more data is needed for a significant improvement of mixture modelling and elucidation of drivers of toxicity. This database will be essential to reveal CEC-induced bioassay activity that cannot be explained by the measured concentrations of the few individual chemicals for which effect data are already known [41]. Other needs and purposes for this database, e.g. selection of EBMs, are currently being explored within the NORMAN network.
Support to national and European chemical risk assessment: harnessing, combining and sharing evidence and expertise on CECs Cross□border cooperation and information exchange—
monitoring super□sites in Europe
Perspectives and recommendations Organise Europe-wide collaborative environmental monitoring programmes using novel analytical methodologies
in a broad range of matrices and on selected super-sites providing representative geographical coverage and results directly supporting regulations.
Improve the sharing and use of local, regional, national and EU-level monitoring data between countries and policy areas (e.g. legislation for environment, chemicals, food, products, waste, etc.) and relevant institutions.
Rationale All state-of-the-art tools presented here have been developed and tested within large-scale European projects (e.g. FP7 SOLUTIONS, EDA-EMERGE FP7-PEOPLE-2011-ITN/290100, ANSWER H2020MSCA-ITN-2015/675530, NEREUS COST Action ES1403, APEX LIFE17 ENV/SK/000355).

NORMAN works in close cooperation with international river basin organisations (e.g. the International Commission for the Protection of the Danube River (ICPDR) ± 14 European countries and the EU; organising Joint Danube Surveys every 6 years), sea conventions (e.g. Black Sea Commission; OSPAR), environmental specimen banks and environmental authorities in various Member States (e.g. France, Germany, Nordic countries, The Netherlands).
In 2019 the NORMAN Association received funding from the ICPDR as a contribution in support of its participation in the experimental activities of the 4th Joint Danube Survey (JDS4). The added value of this type of collaboration is the opportunity to investigate and demonstrate the capabilities and limits of new environmental assessment frameworks with a clear link to their application in a regulatory framework.
So far, NORMAN has been strongly involved in issues related to CECs in the fresh water cycle and the associated EU policies. In the light of NORMAN's missions and the need to ensure a holistic view of emerging risks associated with chemicals in the environment, the activities are progressively being extended to the indoor, marine and terrestrial environment and water reuse, thereby building on experience gained in the water compartment to facilitate the transfer to other environmental matrices.
Conclusions Scientific knowledge continues to progress, and novel tools are constantly being developed. This helps competent authorities and industry in the full value chain of chemicals to provide answers to unanswered or newly arising questions regarding risks of chemicals to the environment and human health, with a particular focus on early warning, anticipation and prevention of future risks.
In this paper, we have sought to provide a clear and transparent message about how NORMAN as an
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independent, well-established and competent network of expert organisations in the field of emerging substances has enormous potential to contribute to the implementation of the PARC partnership by sharing several of its existing key tools that we believe are particularly relevant to the success of the initiative.
An important role of the PARC partnership will be to foster cooperation and better use of existing knowledge, for better coordination of research and uptake of scientific findings in regulation.
NORMAN stands ready to provide expert advice to PARC's stakeholder forum, drawing on its 15 years of experience in the development, harmonisation and testing of advanced tools in relation to CECs and in support of a European Early Warning System to unravel the risks of CECs and close the gap between research and innovation and regulatory processes. NORMAN is a platform for scientific cooperation building upon voluntary member contributions to advance our knowledge and understanding of CECs in the environment. By combining the extensive knowledge and experience of the NORMAN network with the financial and policy-related strengths of the PARC initiative, a large step towards the goal of a non-toxic environment can be taken.
Abbreviations ARB: antibiotic-resistant bacteria; ARG: antibiotic-resistant genes; BCF: bio concentration factor; CAS: chemical Abstracts Service; CEC: contaminants of emerging concern; CEN: European Committee for Standardization; CEN TS: CEN Technical Specifications; CIS: Common Implementation Strategy of the WFD; DG ENV: Directorate-General for Environment of the European Com mission; DG Research: Directorate General for Research and Innovation of the European Commission; EBM: effect-based methods; EBT: effect-based trigger values; EC: European Commission; ECHA: European Chemical Agency; EC JRC: Joint Research Centre of the European Commission; EDA: effect-directed analysis; EEA: European Environment Agency; EQS: environmental quality standard; ICPDR: International Commission for the Protection of the Danube River; IPCHEM: European Information Platform for Chemical Monitoring; JDS: Joint Danube Survey; NTS: non-target screening; PNEC: predicted no-effect concentration; RBSP: River Basin Specific Pollutants;
WFD: Water Framework Directive.
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Making Waves: Collaboration in the time of SARS-CoV-2 - rapid development of an international co-operation and wastewater surveillance database to support public health decision-making
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abstract
The presence of SARS-CoV-2 RNA in wastewater was first reported in March 2020. Over the subsequent months, the potential for wastewater surveillance to contribute to COVID-19 mitigation programmes has been the focus of intense national and international research activities, gaining the attention of policy makers and the public. As a new application of an established methodology, focused collaboration between public health practitioners and wastewater researchers is essential to developing a common understanding on how, when and where the outputs of this non-invasive community-level approach can deliver actionable outcomes for public health authorities. Within this context, the NORMAN SCORE "SARS-CoV-2 in sewage" database provides a platform for rapid, open access data sharing, validated by the uploading of 276 data sets from nine countries to-date. Through offering direct access to underpinning meta-data sets (and describing its use in data interpretation), the NORMAN SCORE database is a resource for the development
of recommendations on minimum data requirements for wastewater pathogen surveillance. It is also a tool to engage public health practitioners in discussions on use of the approach, providing an opportunity to build mutual understanding of the demand and supply for data and facilitate the translation of this promising research application into public health practice.

1. Introduction
Research continues apace into many aspects of the use of wastewater surveillance for the detection of SARS-CoV-2 and how data generated can be utilised within local public health decisionmaking. Also known as sewage or environmental surveillance, the approach has an established literature in terms of monitoring the occurrence and concentration of chemicals arriving at a wastewater treatment plant (WWTP) (Choi et al., 2018). Determined chemical concentrations, loads and population normalised loads of illicit (González-Mariño et al., 2020a, b; Ort et al., 2014) and licit drugs including tobacco, caffeine and alcohol (Castiglioni et al., 2015; Gracia-Lor et al., 2017; Ryu et al., 2016, Thomaidis et al., 2016) are used to provide quantitative longitudinal data sets on the use at a catchment level. It is also possible to evaluate the rates of exposure to environmental or food contaminants using the same approach (Rousis et al., 2017; Lopardo et al., 2019). Furthermore, wastewater surveillance can be used to evidence
changes overtime in relation to the implementation of new policy initiatives. The practical utility of chemical wastewater surveillance data sets is demonstrated by its use within local and national monitoring and public health programmes (EMCDDA, 2020; Riva et al. 2020; Lai et al., 2018). Prior to 2020, the use of wastewater surveillance for monitoring pathogens was gaining ground only slowly. Most notably, enterovirus wastewater surveillance systems have been established in several locations (Sedmak et al., 2003; Majumdar et al., 2018), with wastewater surveillance identified as playing a key role in polio eradication schemes in Israel, India and Egypt (WHO, 2020; Ashgar et al., 2014; Holm-Hansson et al., 2017). The first SARS-CoV2 wastewater surveillance studies were undertaken in the Netherlands, with viral RNA material detected in wastewater treatment influent samples in seven Dutch cities and the international airport
(Medema et al., 2020a). This landmark study included data on the detection of viral fragments in wastewater in one city prior to the detection of any clinical cases. This potential to provide an early warning on the presence of the virus within a community is a proof-of-concept and an evidence base that could be used by public health teams as a trigger to intensify clinical testing, facilitating the identification and isolation of positive cases (Thompson et al., 2020; POST, 2020). Hence, the use of wastewater surveillance for SARS-CoV-2 as a tool to address the COVID19 pandemic is a new application of an established method in a rapidly moving field.
SARS-CoV-2 wastewater surveillance studies to date have demonstrated the occurrence of its RNA genome in a range of compartments, primarily WWTP influents but it has also been reported in sludge and effluents as well as within receiving waters (Jones et al., 2020; Randazzo et al., 2020). In terms of infectivity potential of wastewater containing SARS-CoV-2 RNA, initial studies (Westhaus et al., 2021; Bivins et al., 2020a) and expert opinion (WHO, 2020; Jones et al., 2020) indicate that detected RNA materials do not occur in the form of an infectious viral particle. Further studies also looked to establish a quantitative relationship between viral load and number of clinical cases reported within a catchment (Vallejo et al., 2020; Ahmed et al., 2020). However, variations in the load and duration of viral material shed in faeces by asymptomatic, pre-symptomatic and symptomatic cases, together with limited understanding of the fate of viral particles within sewer systems (which vary significantly in design and flow dynamics),
and variations in analytical protocols and their associated extraction efficiencies, generates considerable uncertainty in terms of directly relating viral loads to numbers of cases. Hence, many open challenges exist within this research area and use of data by public health teams. Within the field, key research questions encompass the potential for viral materials to ad-

sorb to biofilm and particles, degrade in the sewage system and optimising sample collection processes, including collection location and frequency (WHO, 2020). Moreover, the need to standardise and optimise analytical protocols has been clearly identified (Michael-Kordatou et al., 2020). In terms of interpreting data, key issues include data comparability between studies (e.g. use of a common marker for normalisation and how contextual data e.g. flow and other parameters are included in data interpretation), the identification of a SARS-CoV-2 RNA threshold value and the actions that exceeding a threshold value should trigger (Medema et al., 2020b). Variations in the amount of viral RNA excreted per person are a further unknown, and inherent levels of variability in shedding may make accurate predictions of prevalence impossible. However, the absence of an absolute understanding of shedding rate behaviour does not preclude the use of this approach in public health contexts, where relative changes in signal (as opposed
to its absolute value) can provide public health teams with valuable data. Further open questions remain over ethical aspects related to the use of wastewater surveillance, and the need to develop a social license to operate if the approach is to be successfully adopted. Whilst ethical aspects have been largely overlooked during the current health emergency, developments in near source tracking e.g. analysis of wastewater from aeroplanes, hospitals and schools (Ahmed et al., 2020; Gonçalvesa et al., 2021; Hassard et al., 2020, Hong et al., 2021) are rapidly pushing this issue up the research and practice agenda. In this article a bottom-up, collaborative approach to enabling researchers to systematically and rapidly share raw data on traditional wastewater parameters, the occurrence of SARS-CoV-2 and clinical case numbers is presented, as both a resource for researchers and a tool to facilitate discussion with public health teams.
2. The use of wastewater surveillance data within public health decision-making

Wastewater surveillance can be used to non-invasively screen ‘hard to test’ communities (i.e. where uptake of testing is low or challenging for resource reasons) at a sewer catchment level as a new public health tool to understand COVID-19 spread (CDC, 2020; POST, 2020). Detection of SARS-CoV-2 RNA fragments in wastewater is independent of clinical testing strategy bias (Thompson et al., 2020), can be used as an early warning of the need for further testing (e.g. reallocating/increasing local testing resources such as drive-through test facilities) or the implementation of wastewater surveillance upstream of the WWTP i.e. near-source tracking to identify location of cases (Hassard et al., 2020). For example, the detection of SARS-CoV-2 RNA concentrations can indicate the (re-) emergence of the virus in a catchment following a period of no clinical cases and an increase in viral RNA load can indicate the occurrence of new outbreaks, requiring the urgent tracing of infected individuals and their subsequent support
to isolate (DEFRA, 2020). Likewise decreasing prevalence can indicate that infected individuals are ‘known’ and isolation/public health interventions are effective. Further, an increase in viral load over time against a trend of ‘no-change’ in daily positive case numbers could indicate that the clinical testing regime should be intensified (i.e. new cases are not being detected) (Thompson et al., 2020). Wastewater surveillance data sets can also be used to evidence the effect of alternative policy actions e.g. curfew vs local lockdown vs national lockdown at a community level, as well as track progress of vaccination campaigns.
To deliver these types of actionable outcomes i.e. to enable public health authorities to use wastewater surveillance data within their community level decision-making processes requires activities on several fronts. As well as addressing the wastewater surveillance methodological and analytical challenges identified
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earlier, data from wastewater needs to be collected frequently and available rapidly in a format that is useful and useable by public health practitioners. Further collaboration between wastewater and public health practitioners is required to ensure that public health teams can access the type of data they require in a timeframe and format that integrates with current pandemic mitigation measures i.e. addressing public health data requirements needs to be front and centre of operationalising this new development in wastewater surveillance. The format and sampling strategies underpinning wastewater data sets may need to morph in terms of the locations and frequency of sample collection, quality assurance/quality control processes, scale at which data is generated and made available and the aspects of primary value from a public health perspective i.e. absolute values or trends analysis. Delivering this type of integrated data share ‘dashboard’ is already challenging under usual working conditions; working across disciplines during a pandemic when public health teams are at (or beyond) full capacity is extremely challenging. However, collaboration between public health and wastewater researchers – where public health practitioners take a lead role in determining dashboard development - is happening. For example, in Australia, the development of a SARS-CoV-2 wastewater surveillance dashboard was led by a collaboration between the Victorian state public health team and Water Research Australia. This has already matured from a research and development phase to an operational tool for day-to-day use with functional dashboards for both internal and external communications (Victoria State Government, 2020). Other countries with established monitoring programs include Canada (https://cwn-rce.ca/covid-19-wastewater-coalition/), Finland (https://www.thl.fi/episeuranta/jatevesi/jatevesiseuranta_viikkoraportti.html),
Luxembourg
(https://www.list.lu/en/covid-19/),
Greece (http://trams.chem.uoa.gr/covid-19/), the Netherlands (https://www.rivm.nl/en/covid-19/sewage), and Spain (https://www.miteco.gob.es/es/agua/temas/concesiones-y-autorizaciones/vertidos-de-aguas-residuales/alerta-temprana-covid19/default.aspx). In the UK, sharing of data between a government-led wastewater surveillance project and the national COVID-19 ‘track and trace’ programme led to the identification of an increase in SARS-CoV-2 RNA in wastewater despite relatively low numbers of people taking clinical tests (DEFRA, 2020). This data was used to alert local health professionals to contact people in the area to warn of the increase in cases and encourage local populations to engage with clinical testing programmes.
The need for and benefits of collaboration among wastewater researchers has been recognised and several international and national collaborations rapidly established (e.g. Bivins et al., 2020b; WRF, 2020; WHO, 2020; JRC, 2020; Réseau Obépine, 2020; WRA, 2020; UCMERCED, 2020). These have focused primarily on technical and analytical issues, facilitating opportunities for rapid

discussion on a range of topics from recent publications to method development, predictive modelling and risk assessment. However, collaboration activities to-date have yet to address two key issues: firstly, the development of an open-access data platform to enable and facilitate the rapid sharing and critical evaluation of multiple wastewater meta-data sets to address technical issues (Bivins et al., 2020a). Secondly, engagement with public health authorities i.e. development of a critical mass of public health and wastewater researchers to collaboratively identify and deliver an operational SARS-CoV-2 wastewater surveillance public health system.

3. Open-access data sharing to progress collaboration across disciplines

The NORMAN/SCORE SARS-COV-2 in sewage (SC2S) database is a platform, which can contribute to meeting both these needs. This open-access database is an output of the collaboration be-

Table 1 Overview of parameters recorded and their role in facilitating data analysis, interpretation and comparison.

Type of data	Parameters	Role in data interpretation
Sampler information Sampling site	SARS-CoV-2 clinical prevalence data	
Sample matrix Sampling date Sampling procedure	Inflow characteristics	
Sample preparation		
RNA extraction		
Analytical method		
RNA concentration / abundance		
Name, contact details WWTP name and country; longitude/latitude; altitude (m)	Design capacity (PE); population served (PE); catchment size (m2)	
No. of people SARS-CoV-2 positive on sampling date		
No. of people recovered from SARS-CoV-2 on sampling date	No. of people SARS-CoV-2 positive 2 weeks prior to sampling date	No. of people recovered from SARS-CoV-2 2 weeks prior to sample date
Influent wastewater		
Start and finish: hour; day; month; year		
Composite (time- or flow-weighted with intervals reported) or grab sample		
Flow (total m3; minimum/maximum m3/h);		
COD [mg/L]; TSS [mg/L]; Total N / NH4-N [mg N/L]		
Rain (dry weather/number of days since last rain event		
Date of analysis; storage temperature (°C)		
Internal standard used (if so which)		
Method used for sample preparation		
Volume of sample [mL]		
Number of replicates		
Date of and method used for RNA extraction		
Genetic markers (N1, N2, E etc.)		
Internal standard used (if so which)		
RNA [µL; ng / µL]		
Number of replicates		
Technique e.g. Conventional PCR / Real-time PCR / Illumina Myseq / Whole genome sequencing / LAMP-PCR / non-targeted analysis.		
Limit of detection (number of copies/mL of sample)		
Limit of quantification (number of copies/mL of sample)		
Uncertainty of the quantification (%RSD)		
Extraction efficiency		
Concentration of RNA in which analysis performed (µL; ng/µL)		
Positive control used (if so which)		
Number of replicates		
Cycle threshold (Ct)		
Gene copy [number/mL of sample or number/ng of RNA)		

Key: WWTP = wastewater treatment plant

Auditability	Identify sewer shed location; consider climatic influences	Consider drainage network size and WWTP loads/dynamics; calculate population density and population-normalised virus loads
Relationship between viral load and clinical cases on day of sampling		
Relationship between viral load and all clinical cases to-date		
Longitudinal trends in clinical case numbers; consider shedding from active cases versus post-infection shedding		
Confirmation of sample type		
Seasonality		
Understanding of sampling errors/bias		
Consider drainage network and WWTP dynamics; calculate mass loads		
Consider effects of wastewater composition on RNA yield and occurrence of groundwater infiltration		
Occurrence of dilution due to rainfall		
Potential for degradation of RNA		
Process quality control / quality assurance		
Potential differences in extraction efficiencies		
Understanding of RNA copies per a certain wastewater volume		
Quality control / quality assurance		
Differences in sensitivity using qPCR analysis		
Quality control / quality assurance in understanding RNA extraction efficiency		
Quantitative identification of virus in wastewater		
Quality control / quality assurance		
Quality control / quality assurance		
The lowest level of virus that can be determined as present		
The lowest level of virus that can be quantified at a good confidence		
Potential variations in qPCR measurement		
Understanding of performance of selected extraction methods		
Quantitative information of virus measured in wastewater extracts		
Process quality control / quality assurance; indication of method performance		
Quality control / quality assurance		
Quality control / quality assurance		
Trend and spatial evaluations of virus levels within and across catchments. Calculations considering concentrations, wastewater flow and population served by a WWTP.		

tween two international networks: the NORMAN network (www. norman-network.net/) of research organisations supporting the validation and harmonisation of measurement methods and monitoring tools and SCORE (https://score-cost.eu) a network established to harmonise methodologies for measuring human biomarkers in wastewater to evaluate lifestyle, health and exposure at the community level. The database is located within the NORMAN Database System at https://www.norman-network.com/nds/ as the latest addition to its 13 database modules within the interlinked database system series for the collection and evaluation of data / information on emerging substances in the environment (Dulio et al., 2020). The SC2S database structure follows that of the NORMAN Antibiotic Resistance Bacteria/Genes database, enabling users to freely access data at a WWTP level as well us upload new data via a customised data collection template (DCT; downloadable from the website) which facilitates its automatic uploading to the system. On accessing

the database, users can search via country and/or WWTP or view the entire data set (both within the database or it can be exported into MS Excel) without any restrictions. Data displayed in the dashboard includes sampling date, gene copy (number of copies/mL and/or ng of RNA/mL), cycle threshold (Ct), WWTP and country name, population served and the number of people reported SARS-CoV-2 positive in the sewer catchment area on the day of sampling. Table 1 identifies the requested reporting parameters and provides an overview of their role in interpreting generated data sets. Finally, the full DCT containing all reported data on all parameters can be downloaded for each dataset. In terms of engaging the attention of public health authorities, as a first step it includes both wastewater and clinical case data. In addition, and perhaps more importantly, it is a starting point for further discussions with public health practitioners on what wastewater surveillance is, the types of longitudinal data sets it can produce (together with process controls), and the potential of this non-invasive approach as a tool to provide an early warning of new clusters as well as the impact of existing pandemic mitigation measures.

Fig. 1. Overview of the number of data sets contributed to the NORMAN SCORE SC2S database per country.

To launch the database, invitations to participate were initially shared through both the NORMAN and SCORE networks, with a request for members to disseminate further through their own networks. To harmonise activities, participants were provided with a common protocol covering sample collection, RNA extraction and analysis. The common protocol (available at https://www.norman-network.com/nds/sars_cov_2/) adopts the Medema et al (2020a,b) methodology with an alternative simplified protocol for SARS-CoV-2 extraction from wastewater via polyethylene glycol (PEG) precipitation (recognising that many consumables/equipment currently in short supply). Given the logistical challenges and urgency to share data quickly, participating laboratories did not undertake an inter- laboratory validation procedure but were asked to report their laboratory QA/QC procedures in full. Submission of data using both methods is welcomed, with space on the DCT to identify which approach was used and the genes targeted. A further step was to establish a 'buddy system' for research groups who were able to collect wastewater samples but whose laboratories were under lock-down and/or were not familiar with RNA analysis. As such, the rapid sharing of a common protocol also had a capacity building effect, enabling many groups to explore opportunities to undertake wastewater surveillance for pathogens for the first time. Two scheduled sampling campaigns were held on June 1st 2020 and June 15th 2020, with data referring to further identified sampling campaigns now welcomed. To date the SC2S database contains 276 sets of data from nine different countries (see Fig. 1).

The impact of pandemic mitigation measures on working conditions impacted on the ability to both collect and manage samples e.g. reduced access to WWTPs and laboratories, consumables and/or work force. Further, whilst the DCTs were developed to support systematic data reporting, not all laboratories were able to provide all requested data due to the on-going challenges experienced by many research groups in terms of access to laboratories, shortages/delays in shipping consumables and reduced work force. Nevertheless, all received data sets were uploaded to achieve the aim of rapid data share as a compliment to ongoing efforts to standardise sampling and analytical protocols. Downloading the current data set shows that 24-hour composite samples (either volume-weighted or time-weighted) were collected on several dates on or close to scheduled sampling dates (from 24th May 2020 – 16th June 2020) with grab and/or composite samples collected on further as local conditions permitted. Sample preparation date, date of analysis and storage conditions were identified, together with the method used for sample preparation, RNA extraction, analysis and the use of internal standards in the sample preparation phase (61% of samples) and the RNA extraction step (88% of samples). Reviewing the data set as a whole, a positive signal for SARS-CoV-2 was quantified in 167 of the 276 samples analysed.

Of these 167 samples, the N1 gene was quantified in 18 samples, N2 gene in 8 samples, a combined measure of N1 and N2 in 133 samples and the E gene in 3 samples. Ct counts ranged from 31.9 - 41.9 (median 35), with the number of gene copies/ml ranging from 0.04 – 148 gene copies/mL (median: 10.6 gene copies/mL). In terms of quality control, reported analysis included two to six replicates per sample with the use of a positive control reported in the analyses of 268 of the 276 samples. The analytical limit of detection was reported on 173 occasions (range: 3 – 5 gene copies/ml for N1 gene; 0.5-5 gene copies/ml for N2 gene; 0.75 gene copies/ml for N1/N2 combined gene measurement; 0.5 - 100 gene copies/mL for E gene), with a study by Philo et al. (2021) suggesting that the variability in detection between target genes could be due to variations in the performance of assays or differential rates of degradation in the target genetic material. No study reported their limit of quantification. In terms of clinical data, the number of positive cases reported in the local municipality (which may/may not reflect the sewer catchment) on the day of sampling was reported for 260 of the 276 samples analysed (range: 0 – 1701; median = 239 cases). Whilst at sewer catchment level, ethical issues around participant anonymity and data protection is generally not an issue. However, as contributing areas reduce to, for example, an individual building level, the need to systematically and robustly consider the use of generated data at source and further downstream (i.e. secondary data use) becomes increasingly urgent.

4. Conclusions

The current data hosted by the SC2S provides a snapshot of the occurrence of SARS-CoV-2 in wastewater at participating WWTPs and demonstrates the ad-hoc cooperation of the scientific community on data collection. However, more importantly, the NORMAN/SCORE initiative:

- demonstrates that the SC2S database is a workable multijurisdictional data-share platform with potential to facilitate development of an international dataset
- provides a tool to engage and inform discussions with public health practitioners on the potential role of wastewater surveillance as an additional approach to integrate within community public health strategies
- is open to all (contributors are warmly invited to submit data from any campaigns they are able to share, using the relevant sections on the DCT to document sample collection, storage and analytical details together with clinical case numbers)
- with continued use, this collection of wastewater meta-data will support a retrospective analysis of the impact of differing sewer/catchment/population variables on the use of wastewater surveillance as a tool in public health practice

• facilitated the collection of comparable data sets from an early phase of the pandemic; continued use will provides an opportunity to maximise operational insights gained during different phases of the pandemic and support development of robust best[2488»]practice in wastewater surveillance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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RESEARCH
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The NORMAN Suspect List Exchange (NORMAN-SLE): facilitating European and worldwide collaboration on suspect screening in high resolution mass spectrometry
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Abstract
Background: The NORMAN Association (https://www.norman-networ k.com/) initiated the NORMAN Suspect List Exchange (NORMAN-SLE; https://w ww.norman-network.c om/n ds/S LE/) in 2015, following the NORMAN collabora- tive trial on non-target screening of environmental water samples by mass spectrometry. Since then, this exchange
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of information on chemicals that are expected to occur in the environment, along with the accompanying expert knowledge and references, has become a valuable knowledge base for "suspect screening" lists. The NORMAN-SLE now serves as a FAIR (Findable, Accessible, Interoperable, Reusable) chemical information resource worldwide.
Results: The NORMAN-SLE contains 99 separate suspect list collections (as of May 2022) from over 70 contributors around the world, totalling over 100,000 unique substances. The substance classes include per- and polyfluoroalkyl substances (PFAS), pharmaceuticals, pesticides, natural toxins, high production volume substances covered under the European REACH regulation (EC: 1272/2008), priority contaminants of emerging concern (CECs) and regulatory lists from NORMAN partners. Several lists focus on transformation products (TPs) and complex features detected in the environment with various levels of provenance and structural information. Each list is available for separate down- load. The merged, curated collection is also available as the NORMAN Substance Database (NORMAN SusDat). Both the NORMAN-SLE and NORMAN SusDat are integrated within the NORMAN Database System (NDS). The individual NORMAN-SLE lists receive digital object identifiers (DOIs) and traceable versioning via a Zenodo community (https:// zenodo.o
rg/communities/n orman-sle), with a total of > 40,000 unique views, > 50,000 unique downloads and 40 citations (May 2022). NORMAN-SLE content is progressively integrated into large open chemical databases such as PubChem (https://p ubche m.n cbi.nlm.nih.g ov/) and the US EPA's CompTox Chemicals Dashboard (https://compto x. epa.g ov/d ashbo ard/), enabling further access to these lists, along with the additional functionality and calculated properties these resources offer. PubChem has also integrated significant annotation content from the NORMAN-SLE, including a classification browser (https://pubche m.ncbi.n lm.nih.g ov/c lassi fica tion/#h id=101).

Conclusions: The NORMAN-SLE offers a specialized service for hosting suspect screening lists of relevance for the environmental community in an open, FAIR manner that allows integration with other major chemical resources. These efforts foster the exchange of information between scientists and regulators, supporting the paradigm shift to the “one substance, one assessment” approach. New submissions are welcome via the contacts provided on the NORMAN-SLE website (https://w ww.n orman-network.com/nds/SLE/).
Keywords: Suspect screening, High resolution mass spectrometry, Non-target screening, Open science, FAIR (Findable Accessible Interoperable Reusable) data, Data exchange, Cheminformatics, Exposomics, Environmental contaminants, Chemicals of emerging concern

Background In environmental analytical chemistry, suspect screening typically involves the use of high resolution mass spectrometry (HRMS) to search for the presence of chemicals in environmental samples based on suspect lists, using the exact mass as a first step in the annotation of detected features [1, 2]. Suspect screening has grown in popularity over the last few years as an efficient way to complement traditional target analysis approaches, where a reference standard is required, without performing a time-intensive non-target screening of the tens of thousands of unknown features typical in environmental samples using extensive compound databases. Several publications describe these approaches in greater detail [1–4]. The NORMAN Association (a network of reference laboratories for monitoring of contaminants of emerging concern (CECs) in the environment—hereafter “NORMAN”) [5] ran the first non-target screening (NTS) collaborative trial on river water in 2013/2014 [4]. The results showed that participants

tentatively identified roughly as many chemicals via both suspect and target screening methods, but very few via NTS [4]. This early effort demonstrated that suspect screening approaches were

more efficient and popular across the 19 participating institutes, offering a much higher annotation rate than non-target identification. Since then, NORMAN has run further collaborative trials involving suspect screening, including dust [6], passive samplers [7] and biota [8]. Suspect screening has also gained popularity beyond environmental studies and matrices, expanding recently to biomonitoring (e.g., [9, 10]).

One major outcome of the 2013/2014 NORMAN NTS collaborative trial was the clear need for a better exchange of chemical information both among and beyond NORMAN members [4], since the 2013/2014 collaborative trial participants used an incredibly wide variety of data sources during the trial (shown in Table 3 of [4]). This need had already been identified earlier, for example in the MODELKEY project [11] that included several NORMAN members, but the right implementation strategy remained elusive. A second NTS collaborative trial outcome, discussed in subsequent workshops, was a debate between “screen smart”, versus “screen big”. At the time, the “screen smart” strategy had been employed, for example, to study pesticides [12], pharmaceuticals [13] and surfactants [14] using relatively small lists (185, 980 and 394 entries, respectively), to support

focussed research questions. In contrast, the “screen big” strategy used very large lists containing thousands of chemicals (e.g., lists of high production volume chemicals registered under the European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation (EC No 1272/2008)) to find more hits—with the accompanying risk of many more false positives (see e.g., [15, 16]). Naturally, the boundary between these two strategies blurred over time, as some “smart” suspect lists also became quite “big”. For instance, the STOFFIDENT (https://water.f or-ident.o rg/#! home) compilation of water-relevant contaminants such as pesticides, pharmaceuticals and industrial chemicals [17] includes over 10,500 substances. This list is “smart” with respect to the relevance to the water compartment, but with many pollutant classes and a large proportion of REACH chemicals, the overall number of chemicals is large enough to increase the probability of generating many false-positive results. In the

extreme, “screen big” could be extended to candidates from even larger compound databases with millions of entries, which are commonly used in NTS approaches—with the lower success rates (i.e., more false positives) as mentioned above. Since suspect screening approaches typically start with only an exact mass of the expected adduct(s) of the suspects, there is a large burden of proof to confirm that the “suspect hit” is actually present, as discussed elsewhere [2–4].

The exchange of and access to chemical information in an open (i.e., free to access, publicly available) manner [18] has not always been as easy as it appears today. A key breakthrough was achieved in 2004 with the launch of PubChem (https://p ubche m.ncbi.nlm.n ih.g ov/) [19], currently one of the largest open chemical knowledge bases with extensive information on over 111 million chemicals (July 2022). The ChemSpider collection was released a few years later (http://www.c hemspider.com/) [20] and now contains 114 million chemicals (July 2022). The United States Environmental Protection Agency (US EPA) released the CompTox Chemicals Dashboard (https://compto x.e pa.g ov/dashbo ard/) [21] (hereafter “CompTox”) in 2016 as a smaller collection, currently of 906,511 chemicals (July 2022) related to environmental and toxicology questions. Likewise, in 2016 the term “FAIR” was coined, describing how to make research more Findable, Accessible, Interoperable and Reusable [22, 23]. Together, ensuring that

data is both Open and FAIR is a powerful combination [24]. The European Union (EU) is also embracing Open and FAIR principles. The European Chemicals Agency (ECHA) [25] and the European Food and Safety Authority (EFSA) [26] are transitioning their information to be more Open and FAIR, while Joint Research Centre (JRC) has released the Information Portal for Chemical Monitoring (IPCHEM)

for the exchange of monitoring data in Europe [27]. Recent initiatives such as the European Partnership for Chemicals Risk Assessment (PARC) [28, 29] and the Environmental Exposure Assessment Research Infrastructure (EIRENE) [30] will strengthen this into the future.

In response to the NORMAN NTS collaborative trial outcomes, NORMAN initiated the NORMAN Suspect List Exchange (NORMAN-SLE, https://w ww.n orman- networ k.com/nds/SLE/) in 2015 as part of the NORMAN Database System (NDS, https://www.n orman-n etwor k. com/n ds/) [29, 31] to facilitate the open access exchange of various suspect lists within and beyond Europe. This FAIR, open access, whole community initiative is not limited to NORMAN members. The primary aim of the NORMAN-SLE is to provide a location where suspect lists are publicly accessible, together with appropriate reference information, for interested parties to browse and select as desired (facilitating the “screen smart” approach). The NORMAN-SLE forms the basis for the NORMAN Substance Database (NORMAN SusDat, https://www.norman-networ k.c om/nds/susdat/), a merged and curated data table with additional parameters for use in NORMAN activities (to facilitate the “screen big” approach), which will be described in more detail in a separate

article. The present article covers the creation and implementation of the NORMAN-SLE as an Open and FAIR data resource, along with its integration with major open chemistry resources (PubChem, CompTox) as described below in the methods section, followed by an overview of the current state, implications and outlook in the results and discussion sections.

Methods NORMAN Suspect List Exchange (NORMAN SLE) website The principle behind the NORMAN-SLE is simple: facilitating the exchange of chemical information to support the suspect screening of primarily organic contaminants amenable to liquid or gas chromatography (LC or GC) coupled to mass spectrometry. The website itself (https:// www.n orman-network.c om/n ds/S LE/) contains a simple overview of the background behind the NORMAN-SLE and a table containing the suspect lists themselves (with the fields “Number”, “Abbreviation”, “Description”, “Link to full list”, “Link to InChIKey list” and “References”), as shown in Fig. 1 and explained further below. Each list has a number (starting with S0 for SUSDAT, the merged collection), increasing sequentially with every contribution, along with an abbreviation for easier integration, access, and recognition.
The idea behind the simplicity of this website is to enable public access to various suspect lists as close as

Fig. 1 Screenshot of the NORMAN Suspect List Exchange (https://www.n orman-network.com/n ds/S LE/) [32]
possible to the lists used in original publications, but with a reasonable degree of standardization and, where possible, added value to enhance and FAIRify these lists for future use (see below). If major adjustments were made to a submitted list, the original list is provided along with modified versions, so that both sets of information are available.
Information content and preparation of suspect lists hosted on the NORMAN SLE The minimum information available in most lists is a name and at least one additional identifier, although in most lists, far more information is available. At least one chemical name (plus other synonyms if available) should be included. The preferred formats for structural information are the simplified molecular-input line-entry system (SMILES) [33] plus the International Chemical Identifier (InChI) in the form of standard InChI and InChIKey [34]. Common database identifiers provided typically include one (or more) of either Chemical Abstract Service (CAS) number(s) [35], EC number [36], PubChem Compound Identifier (CID) [19], ChemSpider identifier (CSID) [20] and/or the Distributed Structure-Searchable Toxicity (DSSTox) substance identifier (DTXSID) used in CompTox [21]. To support suspect screening, the (neutral) monoisotopic masses and molecular formulae are included in many of the lists. This information, along with several other
predicted values, is also included in the merged NORMAN SusDat. Several other fields may be present, depending on the context of the suspect list, and are included where available. More
details on the chemical structure identifiers and recommended chemical structural data templates are provided elsewhere [24, 37].
The suspect lists (commonly submitted via email to NORMAN contact points, see Fig. 2, top left) are processed upon submission, with the subsequent processing steps highly dependent on both the type of submission and the size of the list. While the suspect list number is assigned sequentially, the abbreviation, name and description are assigned following pre-defined conventions, and in discussion with authors. Where necessary, curation is performed on these lists to fill in missing values where at least a chemical identifier and/or structural information and/or (correct) name was provided. For some lists, the missing values are filled using automated workflows covering a variety of web services (depending on the list and contributor) from PubChem [19], ChemSpider [20] and CACTUS (https://c actus.nci. nih.gov/), typically via RMassBank [38], RChemMass [39] and other related packages in the R programming language. Other lists are processed with batch services offered through PubChem [19, 40] and CompTox [21,
41]. Additional chemical structure interconversions (e.g., SMILES to InChI) are performed with OpenBabel (http://openbabel.org/) [42] or the Chemistry Development Kit (CDK) (usually via R) [43] where necessary. Note that the curation performed on the individual suspect lists is independent of the curation and merging to form the NORMAN SusDat collection (see Fig. 2, bottom left), which will be detailed in a separate publication. The processes evolve over time as new technical possibilities

Fig. 2 Schematic showing the relationships between submitted suspect lists, the NORMAN-SLE and downstream resources. Top (orange shading): suspect lists submitted in various formats are curated, then added to the NORMAN-SLE website (centre) and archived on the NORMAN-SLE Zenodo community (top right), yielding a DOI and use statistics. Bottom left (green shading): the NORMAN-SLE serves as an information source for NORMAN SusDat and the NORMAN Database System (NDS). Bottom middle (pink shading): NORMAN-SLE lists are integrated in CompTox manually. Bottom right (blue shading): NORMAN-SLE content is harvested from Zenodo via mapping files and integrated into PubChem in an automated workflow
arise (e.g., batch searching). The resulting suspect lists are generally provided as Excel (XLSX) and comma separated values (CSV) formats, as standardized as reasonably possible, on the website. The CSV format provides greater interoperability, including allowing import into various libraries, vendor and open software, as well as PubChem (described below). A separate InChIKey file is also provided, as this allows fast screening of suspects within the in silico fragmenter MetFrag [44] and other approaches. For some of the lists, additional files are provided, to disseminate all the relevant details. Finally, references and additional information are given, to acknowledge contributors, but also to provide users quick access to the rationale behind each individual suspect list. Further details on the NORMAN-SLE contents, including references, are given in the Results section.
Several suspect lists contain partial, incomplete, or even no structural information, such as the per- and polyfluoroalkyl substances (PFAS) lists S9 PFASTRIER [45] (e.g., elemental compositions retrieved from patents where no structural or isomer information was available) and S46 PFASNTREV19 [46, 47] (a compilation of PFAS identification efforts in non-target screening studies), as
well as the surfactant isomer list S18 TSCASURF [48]. Nevertheless, these lists still provide vital information for identification by mass and/or molecular formula (see e.g., [14, 49], where whole surfactant classes can be identified via the general formula of a homologous series of several structural isomers). For those lists with partial information, missing values were filled in, where possible, as described above, and were saved in separate files or as multiple sheets in one file. Associated InChIKey lists were only generated for known structures. Dealing with partially characterized molecular features or chemical substances of Unknown or Variable Composition, Complex Reaction Products or Biological Materials (UVCB substances, UVCBs) is a subject of future collaborations beyond the scope of the current article (see e.g., [50, 51]), as discussed further below.
NORMAN SLE on Zenodo The development of the Zenodo repository [52] enabled public archiving, versioning and generation of a Digital Object Identifier (DOI) for each NORMAN-SLE list. Thus, since 2019, the NORMAN-SLE content has been uploaded to and archived on the Zenodo repository [52],

gathered under the NORMAN-SLE community (https:// zenodo.org/commun ities/norman-sle/) [53]. Each individual NORMAN-SLE collection has its own Zenodo record and thus a dataset DOI, allowing users to cite the individual lists directly, including specific versions, or all versions. Updates to lists can thus be tracked under the Zenodo version control system, with the master DOI always redirecting to the latest version. The lists are tracked under a versioning system following the pattern NORMAN-SLE-SXX-0.Y.Z, where SXX refers to the list number (as on the NORMAN-SLE website and as described below) and the 0.Y.Z pattern records whether it was a major update (Y is increased incrementally by 1) or minor update (Z is increased incrementally by 1). The leading "0" is currently a buffer. Major updates constitute new entries (e.g., new chemicals, rows, information, updates) to the lists, while minor updates are corrections or adjustments to the current contents without adding major new content (e.g., correcting names,
identifiers, typographical errors). The presence on Zenodo has enabled better citation, the tracking of use statistics at an individual list level and additional possibilities for the integration with external resources such as PubChem, as shown in Fig. 2 (right) and discussed further below. Figure 3 shows the presence of the NORMAN-SLE on Zenodo, including versioning in the inset.

NORMAN SLE and CompTox Chemicals Dashboard integration

Since CompTox [21] is a highly relevant resource for environmental and toxicological information, integration of NORMAN-SLE content is of interest to both parties and is achieved via the "Chemical Lists" functionality (https://comptox.epa.gov/dashboard/chemical-lists/). The integration started in 2017 and is performed through the upload of the DTXSIDs associated with the individual NORMAN-SLE lists to the DSSTox database [55] that underlies CompTox. Most lists have the NORMAN keyword associated with it, such that they are accessible through the URL https://comptox.epa.g ov/dashbo ard/ chemical-l ists?search=N ORMAN, or through a direct URL composed of the list code (e.g., https://c ompto x. epa.gov/d ashboard/chemic al-lists/B ISPHENOLS for the S20 BISPHENOLS list). Several lists on the NORMANSLE were produced in a collaborative curation effort (e.g., S24 HUMANNEUROTOX [56], S37 LITMINEDNEURO [57] and S43 NEUROTOXINS [58], as part of [59]), or were curated and registered by the DSSTox
curation team before uploading to the SLE (e.g., S25 OECDPFAS [60–62]). Some other lists on the NORMAN-SLE were sourced directly from CompTox as they contained entries highly relevant for the NORMAN Database System (e.g., S45 SYNTHCANNAB [63] and S58 PSYCHOCANNAB

Fig. 3 The NORMAN Suspect List Exchange Zenodo community (https://z enodo.o rg/c ommun ities/n orman-sle) with inset showing the versioning history of S36 UBAPMT (https://d oi.org/1 0.5281/z enodo.2 653212) [53, 54]

[64]). For recent lists, generally the CompTox batch search (https://c ompto x.epa.g ov/d ashboard/batch-search) [65] is used to retrieve DTXSIDs on the basis of the user-provided information, which are then provided directly to CompTox along with the list code, name and description for upload. The presence of compounds in NORMAN-SLE lists appear on the individual chemical records in CompTox (see pink entries in the inset in Fig. 2) and can also be identified by prefiltering in the CompTox batch search interface and including flags in the export files.

Due to the infrequent release of updates to CompTox, it may be many weeks or months before new NORMAN-SLE lists are available publicly on CompTox. Currently, 88 of the 99 NORMAN-SLE lists are on CompTox (see Additional file 1), with 74 listed under the "NORMAN" URL above. Since not all substances in the NORMAN-SLE are currently present in CompTox, the mapping of NORMAN-SLE lists in CompTox is often incomplete, i.e., the lists on CompTox contain only entries for which DTXSIDs currently exist (further details are provided in Additional file 1).

NORMAN SLE and PubChem integration

As one of the largest open chemical databases with millions of monthly users, integration of NORMAN-SLE content in PubChem has great potential to increase the visibility of this community effort. The NORMAN-SLE integration with PubChem [19] (https://p ubchem.ncbi. nlm.nih.g ov/) commenced in 2019. The first substance deposition was processed on November 22, 2019. The deposition file is compiled from all lists by the PubChem team, via a mapping file hosted on the Environmental Cheminformatics (ECI) group (University of Luxembourg) GitLab pages [66]. This mapping file contains a link to the latest version of each suspect list (CSV file) on Zenodo, the list details and version, the dataset DOI, extra DOIs (to include related publications), mappings to the columns containing the chemical identifiers (SMILES, InChIKey, InChI, Synonym), the NORMANSLE URL and a comment field. The compiled deposition file is mapped to PubChem Substance Identifiers (SIDs) and PubChem Compound Identifiers (CIDs) via the PubChem deposition
system. While SIDs are available for all substances deposited to PubChem (including those with undefined structures), CIDs are only available for all unique chemical structures (i.e., defined chemical structures) extracted from substance depositions via the PubChem standardization process [67]. As a result, the number of compounds (CIDs) will generally be less than the number of substances (SIDs). Any SMILES errors found during deposition are debugged in collaboration with the PubChem team and any dataset-specific causes

are fixed in the corresponding NORMAN-SLE datasets by releasing new minor versions on Zenodo (see e.g., descriptions in [68, 69]). Synonyms are currently provided as a small, manually curated file containing the columns CID, InChIKey, Synonym, Reference DOI and Dataset information (114 entries on 30 April 2022, see [70]) to specifically add missing synonyms to PubChem [70]. These are primarily newly deposited structures (i.e., structures not yet in PubChem) associated with S74 REFTPS [71] and S96 ECIPFAS [72]. The PubChem/ NORMAN-SLE deposition is re-run once updates are available and takes minutes to run. The updated data are live on the public PubChem website within hours to days (newly added structures can take longer to index fully). The latest deposition and number of live substances (i.e., the number of substances currently available on the public website) can be retrieved from the NORMAN-SLE data source page in PubChem [73].

The contents of individual NORMAN-SLE lists are available interactively in PubChem via the NORMAN Suspect List Exchange Tree (https://pubchem.ncbi.n lm.nih.g ov/ classificat ion/#hid=101, hereafter "PubChem NORMANSLE Tree") on the PubChem Classification Browser [74]. This is compiled by PubChem from a second mapping file, also hosted on the ECI GitLab pages [75]. For each dataset, this mapping file contains a link to the latest InChIKey file on Zenodo, the list title as it should appear in the tree (e.g., "S00 | SUSDAT | Merged NORMAN Suspect List: SusDat") and a tool tip, i.e., further details about the list that displays when users click the "?" icon on the Classification Browser (see figure in Results section). The mapping file also contains additional fields defining the content of interest (keywords, annotations) and other information for internal housekeeping. All lists (except S18 TSCASURF, for which no InChIKeys exist) are listed in numerical order in the PubChem NORMANSLE Tree. In addition,

certain lists with detailed classification content appear again at the top of the browser. These are mapped via structural information in the CSVs (not the InChIKey files) to profit from the detailed additional information available in these lists. The PubChem Classification Browser can also be accessed programmatically (i.e., in an automated manner), with documentation available on PubChem [67] and the ECI GitLab pages [76]. The PubChem NORMAN-SLE Tree also enables users to download individual lists (or even various combinations thereof via advanced queries) in the variety of formats offered by PubChem, including the structure data format (SDF) not currently offered on the NORMAN-SLE website, see documentation available in e.g., [77].

PubChem has also integrated several categories of annotation content, i.e., detailed information about individual chemicals, into the compound records in PubChem. As of

30 April 2022, a total of 17 annotation categories, which equate to headers in the Table of Contents entries in PubChem [78], were integrated. Many relate to the chemical role or use (e.g., the Anatomical Therapeutic Chemical (ATC) Code for pharmaceuticals, Agrochemical Category, Chemical Classes, Use Classifications and Uses) and transformation information (e.g., included in the Transformations, Metabolism/Metabolites, Drug Transformations and Agrochemical Transformations headers). Others relate to chemical information (e.g., molecular formula) and measurement data, such as nuclear magnetic resonance (NMR—13C, 19F, 1H, and 31P), tandem MS (MS/MS) data and collision cross section (CCS) data from ion mobility experiments. Finally, taxonomy information (functionality recently added to PubChem [79] for organisms) has been included for some lists. All files necessary for the integration of the annotation content within PubChem are present in the Zenodo repository for the respective list, supported by additional mapping

or annotation files either added in Zenodo, or hosted on the ECI GitLab pages in the "annotations" subfolder [80] where necessary. The latest overview and the entire content integrated in PubChem (in JSON, XML and ASNT formats, accessible programmatically or for download) is available from the NORMAN-SLE data source page in PubChem [73].

Results

Overview of NORMAN SLE

The NORMAN-SLE includes 99 contributions (starting at S0 SUSDAT, the compilation of all NORMAN-SLE lists, to S98 TIRECHEM) from over 70 contributors as of May 2022, summarized in Fig. 4 and Table 1. Full details on all lists are available in Additional file 1 [81], including list details and chemical numbers across the resources in CSV format, and Additional file 2 [82], a May 2022 copy of the NORMAN-SLE website contents.

Figure 4 and Table 1 show the number of entries in each NORMAN-SLE list as present on the NORMANSLE website and in the latest versions on the NORMANSLE Zenodo collection as of May 2022. The number of InChIKeys associated with these lists (as of May 2022) is available in Additional file 1 [81]. Additional file 1 also includes the number of entries included in PubChem (obtained via the PubChem NORMAN-SLE Tree [74]) and CompTox (via both the CompTox Chemical Lists [232] website as well as via the PubChem EPA DSSTox Tree [233], since the latter can be automated). These statistics were compiled on 4 May 2022. The corresponding files and code are available at the ECI NORMAN-SLE GitLab repository [234] in the "stats" subfolder. Note that the addition of new content to the NORMAN-SLE was put on hold during compilation of this manuscript (May

and June 2022), to ensure that the results included here are internally consistent. All statistics presented here reflect the data in this state. Updates resumed 28 June 2022 and will be described in later efforts (see "Future updates" below).

Summary statistics of the NORMAN SLE

A selection of summary statistics and facts for the NORMAN-SLE is given in Table 2. Both the list and citation information were summarized on 4 May 2022 and the NORMAN-SLE PubChem numbers on 12 May 2022. The (cumulative) numbers of unique views and downloads collected from the NORMAN-SLE Zenodo community on 28 April 2022 are summarized in Table 3, along with the citation numbers for all lists and for the 5 most popular lists according to unique views. The "total unique compounds" number indicates how many entries have a defined chemical structure in PubChem, i.e., a PubChem CID. The "total live substances" number indicates how many entries are deposited, i.e., with a PubChem SID. The total number of unique compounds in PubChem is currently larger than S0 SUSDAT due to the different timing associated with the release cycle of NORMAN SusDat (the basis for S0 SUSDAT), as well as differences in the mappings of structures to unique identifiers. Future efforts will aim to close

this time gap between NORMAN-SLE and NORMAN SusDat (see "Future updates" below). The data files supporting these statistics, including a breakdown of the DOIs of the citing articles, are archived on the ECI NORMAN-SLE GitLab pages [234] ("stats" subfolder) and are available as Additional file 3 [235] (views, downloads, citations per list) and Additional file 4 [236] (more detailed citation breakdown).

In total, 24 of the SLE lists have citations listed in Zenodo, with 40 citations from 19 articles. A full breakdown is given in Additional file 4 [236]. Of these 19 articles, 12 can be considered "internal", i.e., articles written by authors involved with the NORMAN-SLE, including 5 articles describing SLE datasets [59, 118, 149, 154, 174] and 7 others citing SLE lists [24, 142, 237–241], while 7 articles are external [242–248]. Of the 24 lists cited, 6 lists are cited by external authors: S0 SUSDAT, S13 EUCOSMETICS, S14 KEMIPFAS, S25 OECDPFAS, S46 NTPFASREV19 and S75 CyanoMetDB.

NORMAN SLE PubChem integration As described above, the NORMAN-SLE content has been integrated into PubChem in a variety of ways. The basis of all further integration is the substance depositions, formed from the compilation of all lists as described in the Methods section. As of 12 May 2022, the substance deposition in PubChem included 117,071 substances
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Fig. 4 Starburst plots of the 99 suspect lists forming the NORMAN-SLE contents. Lists with: (A) > 8000 entries; (B) 1700–8000 entries; (C) 800–1700 entries; (D) 300–800 entries; (E) 95–300 entries and (F) < 95 entries (ranges chosen to optimize plotting). The list codes, numbers of chemical entries
and references are summarized in Table 1 according to the same groups, with full details in Additional file 1
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Table 1 Summary of the NORMAN-SLE datasets, split by the groups shown in Fig. 4, with suspect list number (S), code, number of entries (lines in the file, in italics) and the accompanying references
Group
List number, Code, Entries (total lines) and References
(A) > 8000
S0 SUSDAT 109,631 [69, 83]; S71 CECSCREEN 70,397 [84, 85]; S32 REACH2017 68,679 [86]; S17 KEMIMARKET 50,308 [68]; S77 FCCDB 12,285 [87–89]; S2 STOFFIDENT 11,289 [17, 90]; S19 MZCLOUD 8742 [91]; S55 ZINC15PHARMA 8646 [92–94]
(B) S33 SOLUTIONSMLOS 6463 [95–97]; S27 KWRSJERPS2 5702 [98, 99]; S89 PRORISKPFAS 4777 [100, 101]; S25 OECDPFAS 4725 [60–62]; S38 1700–8000 SOLNSLMCTPS 4465 [96, 97, 102]; S49 CPPDBLISTB 3353 [103–105]; S13 EUCOSMETICS 3333 [106–108]; S70 EISUSGCEIMS 3266 [109]; S73
METXBIODB 3148 [110, 111]; S14 KEMIPFAS 2602 [112, 113]; S21 UATHTARGETS 2466 [114, 115]; S1 MASSBANK 2305 [38, 116, 117]; S75 CYANOMETDB 2124 [118, 119]; S35 INDOORCT16 2056 [6, 120]; S50 CCSCOMPEND 1983 [121–123]; S80 PFASGLUEGE 1926 [124, 125]; S22 EPACONS 1705 [126, 127]
(C) 800–1700
S60 SWISSPEST19 1664 [128, 129]; S3 NORMANCT15 1662 [4, 130]; S29 PHYTOTOXINS 1586 [131, 132]; S87 CHLORINETPS 1470 [133, 134]; S31 WRTMSD 1429 [135, 136]; S84 UFZHSFPMT 1310 [137–139]; S16 FRENCHLIST 1256 [140]; S37 LITMINEDNEURO 1243 [57, 59]; S53 UFZWANATARG 1235 [141]; S82 EAWAGPMT 1162 [142, 143]; S23 EIUBASURF 1154 [144]; S39 KEMIWWSUS 1123 [145]; S72 NTUPHTW 1068 [146, 147]; S46 PFASNTREV19 1030 [46, 47]; S10 SWISSPHARMA 1020 [13, 148]; S18 TSCASURF 985 [48]; S61 UJICCSLIB 970 [149, 150]; S15 NORMANPRI 967 [151]; S48 CPPDBLISTA 902 [103, 105, 152]; S51 WRIGCHRMS 892 [153]; S76 LUXPHARMA 816 [154, 155]
(D) 300–800
S42 HDXNOEX 765 [156, 157]; S9 PFASTRIER 746 [45]; S6 ITNANTIBIOTIC 676 [158, 159]; S4 UJIBADE 544 [160, 161]; S58 PSYCHOCANNAB 531 [64]; S43 NEUROTOXINS 511 [58, 59]; S66 EAWAGTPS 486 [162, 163]; S34 EXPOSOMEXPL 440 [164–166]; S94 FLUOROPEST 423 [167, 168]; S47 ECHAPLASTICS 418 [169, 170]; S7 EAWAGSURF 410 [14, 171]; S78 SLUPESTTPS 400 [172, 173]; S69 LUXPEST 386 [174, 175]; S36 UBAPMT 341 [54, 176, 177]; S8 ATHENSSUS 340 [49, 178]; S92 FLUOROPHARMA 340 [179, 180]; S65 UATHTARGETSGC 334 [181, 182]; S62 NORMANEWS2 321 [183, 184]; S85 MICROCYSTINS 321 [118, 185]; S79 UACCSCEC 311 [186, 187]
(E) 95–300
S57 GREEKPHARMA 263 [188]; S96 ECIPFAS 258 [72]; S11 SWISSPEST 218 [12, 189]; S54 EFSAPRI 212 [190, 191]; S30 PHENANTIOX 209 [192]; S24 HUMANNEUROTOX 190 [56, 59]; S56 UOATARGPHARMA 185 [193–195]; S28 EUBIOCIDES 160 [196]; S5 KWRSJERPS 159 [99, 197]; S12 NORMANEWS 156 [198, 199]; S26 MYCOTOXINS 149 [200]; S74 REFTPS 146 [71]; S64 NATOXAQ 130 [201, 202]; S91 CECTOYS 126 [203, 204]; S68 HSDBTPS 101 [174, 205]; S86 TATTOOINK 98 [206–208]; S41 CCL4 96 [209, 210]; S83 CCL5 96 [211, 212]; S52 THSMOKE 95 [213]
(F) S95 PFASANEXCH 94 [214, 215]; S63 UBADWGW 84 [176, 216]; S59 NPINSECT 83 [217]; S67 TBUTYLPHENOLS 77 [218]; S97 UBABPAALT 71 < 95 [219, 220]; S88 UBABIOCIDES 62 [221–223]; S93 CECMOUTHING 60 [203, 204]; S40 ALGALTOX 54 [224]; S20 BISPHENOLS 52 [225, 226]; S81 THSTPS 52 [227]; S45 SYNTHCANNAB 39 [63]; S90 ZEROPMBOX1 38 [228, 229]; S44 STATINS 18 [230]; S98 TIRECHEM 16 [231]
Full details given in Additional file 1 and Additional file 2 [81, 82]
(i.e., with PubChem SIDs), mapping to 115,248 unique PubChem CIDs according to the compiled CIDs at the top of the PubChem NORMAN-SLE Tree [74] (see also Table 2). All lists except S18 TSCASURF (for which no InChIKeys are available) are included in the numerically ordered set of lists on the PubChem NORMAN-SLE Tree. As of 30 April 2022, additional detailed classification breakdowns were available for S13 EUCOSMETICS [108], S25 OECDPFAS [60], S36 UBAPMT [54], S47 ECHAPLASTICS [170], S50 CCSCOMPEND [121], S60 SWISSPEST19 [129], S61 UJICCSLIB [150], S66 EAWAGTPS [163], S68 HSDBTPS [205], S69 LUXPEST [175], S72 NTUPHTW [147], S75 CYANOMETDB
[119], S79 UACCSCEC [187] and S80 PFASGLUEGE [124]. Detailed classification content for S77 FCCDB [89] is already drafted on the test site. A screenshot of the top portion of the PubChem NORMAN-SLE Tree is shown on the left in Fig. 5. The collision cross section (CCS) content (S50 CCSCOMPEND [121], S61 UJICCSLIB [150] and S79 UACCSCEC [187]) has also been merged and extended in the “Aggregated CCS Classification” tree on PubChem to combine this with the data from CCSbase [249, 250] and to allow browsing by adduct categories across all datasets [251]. All datasets mentioned here can be accessed via hyperlinks available at the NORMANSLE Data Source page on PubChem [73]. Documentation
Table 2 Selected overall summary statistics for the NORMAN-SLE, compiled in May 2022
Category
Number
Comment
Total number of lists Total unique compounds Total live substances Total live annotations Largest list (# entries) Smallest list (# entries) Total list citations
99 115,248 117,071 21,114 109,631 16 40
S0 to S98 From PubChem NORMAN-SLE Tree [74] From PubChem NORMAN-SLE Data Source Page [73] From PubChem NORMAN-SLE Data Source Page [73] S0 SUSDAT S98 TIRECHEM From NORMAN-SLE Zenodo Community [53]
Further details are given in the “stats” subfolder of the ECI NORMAN-SLE GitLab repository [234]. Total unique compounds = CID count; total live substances = SID count, # entries = number of entries (i.e., rows) in the SLE lists

Table 3 Unique views, downloads and citations for all NORMAN-SLE lists and the Top 5 lists (by unique views), according to the NORMAN-SLE Zenodo Community [53]

List Code	Unique views	Unique downloads	Citations
Top 5 Lists (sorted by unique views) S13 EUCOSMETICS [108]: Cosmetics S60 SWISSPEST19 [129]: Pesticides S72 NTUPHTW [147]: Pharmaceuticals S73 METXBIODB [110]: BioTransformer data S0 SUSDAT [69]: Merged database	10,429	9088	2
Total values All Totals over all lists	2440 2316 2083 503 1858	53,651	3
	2278	2	0
	2043	2	6
	1625	40	

Statistics compiled on 28 April (views/downloads) and 5 May (citations) 2022. The corresponding raw data are given in Additional file 3: Table S3 [235] and on the ECI NORMAN-SLE GitLab pages [234]

Fig. 5 A collage of NORMAN-SLE content in PubChem. Left/back: the PubChem NORMAN-SLE Tree, with entries containing detailed classifications at the top, indicated by the blue arrows. Insets: selected annotation content (Use Classification, Transformations, Taxonomy and Collision Cross Section), linked to the corresponding source list via the green boxes and arrows. Screenshots taken 30 May 2022 (taxonomy on 16 June 2022)

on how to access the data integrated within PubChem is provided on the ECI GitLab pages, including how to find MS [252] and CCS [253] data for NORMAN-SLE lists via PubChem. This also includes code to retrieve the CCS data [254], along with a compiled archive of all CCS values in PubChem (7 June 2022) on Zenodo [255].

In addition to the deposition and classification, extensive annotation content (i.e., expert knowledge) provided within the NORMAN-SLE lists has been integrated within PubChem. Various pieces of information from

NORMAN-SLE lists now appear on the individual compound records for 21,114 compounds (12 May 2022), with several examples shown as insets in Fig. 5. While the presence of this annotation information in text form in individual PubChem records is useful for readers of the individual chemical records, it also helps in search engine optimization (SEO), i.e., the discovery of this information in generalized search engines, beyond the original database. Some categories (PubChem headings indicated in italics) relate to the chemical role, e.g., the “ATC Code”

for pharmaceuticals (from S66 EAWAGTPS [163] and S76 LUXPHARMA [155]), “Agrochemical Category” (S66 EAWAGTPS [163] and S69 LUXPEST [175]), or “Chemical Classes” (S75 CyanoMetDB [119]). Information in the “Use Classifications” and “Uses” categories come from S13 EUCOSMETICS [108], S25 OECDPFAS [60], S47 ECHAPLASTICS [170], S60 SWISSPEST19 [129], S66 EAWAGTPS [163], S69 LUXPEST [175], S72 NTUPHTW [147], S79 UACCSCEC [187] and S80 PFASGLUEGE [124]. The composite “Molecular Formula” representation in S80 PFASGLUEGE [124] is also integrated. Taxonomy information (for organisms) has been included under the “Taxonomy” heading for compounds present in S75 CyanoMetDB [118, 119] and S29 PHYTOTOXINS [132] from the Toxic Plants-Phytotoxins database [131], and also appears on the individual taxa pages.

Transformations for 5135 CIDs have been added from the datasets S60 SWISSPEST19 [129], S66 EAWAGTPS [163], S68 HSDBTPS [205], S73 METXBIODB [110], S74 REFTPS [71], S78 SLUPESTTPS [173] and S79 UACCSCEC [187], as described in some of the articles mentioned above [24, 174, 241]. As a part of this, SEO text snippets describing these relationships have been added to the following headings: Metabolism/Metabolites (S73 METXBIODB [110] and S82 THSTPS [227]), Drug Transformations (S66 EAWAGTPS [163]) and Agrochemical Transformations (S60 SWISSPEST19 [129], S66 EAWAGTPS [163] and S78 SLUPESTTPS [173]). An example Transformations entry is provided in the middle right inset in Fig. 5. The Transformations data are compiled and archived on GitLab [80] and Zenodo [256], and is integrated in patRoon 2.0 [257], an open source software for mass spectrometry based non-target analysis that includes suspect and transformation product screening workflows.

Finally, a significant amount of experimental data has also been included in PubChem from NORMAN-SLE contributors. MS/MS and NMR data have been included from several transformation products (TPs) and/or parent compounds of contaminants of emerging concern, including: 13C NMR, 19F NMR, 1H NMR, 31P NMR, MS/ MS (all from S74 REFTPS [71] containing MS/MS data extracted from 4 articles [258–262] and NMR data from 1 article [258]). Many of these CIDs were not available in PubChem previously. Measured CCS values (often for multiple adducts) associated with 1579 CIDs are included in PubChem, from the datasets S50 CCSCOMPEND [121], S61 UJICCSLIB [150] and S79 UACCSCEC [187] (see also inset at the bottom left in Fig. 5). As mentioned above, this data can be retrieved from PubChem, with documentation provided on the ECI GitLab pages [252–254], along with an archive of the CCS data on Zenodo [255].

Discussion

NORMAN SLE coverage

The NORMAN-SLE (https://w ww.n orman-network. com/n ds/S LE/) provides users with simple access to suspect lists. These lists are then integrated into the merged NORMAN SusDat collection (https://w ww.norman-networ k.c om/n ds/susdat) in the so-called “MSready” [263] form (ready for mass spectral screening, i.e., desalted, neutralized, etc.) with a searchable summary table containing NORMAN-relevant additional properties such as fragmentation information, retention time indices [238] and predicted toxicity values [264]. Over the seven years since the launch of the NORMAN-SLE, the website has grown from hosting a handful of lists to now hosting 99 formal referenced collections, amounting to information on 117,071 substances and 115,248 unique compounds (see Table 2). While these total numbers represent only 0.1% of PubChem contents, it is approximately 12% the size of CompTox, i.e., a significant portion of openly available data on environmentally relevant chemicals. Approximately 43,300 CIDs associated

with the NORMAN-SLE lists are not yet available in CompTox lists (calculated by overlapping the PubChem NORMAN-SLE and US EPA DSSTox trees on 31 May 2022; documented here [265]). A large proportion of these CIDs missing in CompTox come from the European market lists S32 REACH2017 [86] from the REACH regulation and S17 KEMIMARKET from the Swedish Chemicals Agency (KEMI) [68], as well as from S71 CECSCREEN [85]. It is important to note the discrepancy between the NORMAN-SLE and CompTox versions of NORMAN-SLE lists, especially if the European-relevant chemicals are the focus of suspect screening efforts. This discrepancy results, in part, from the fact that it has been challenging to verify the identities of a large number of the REACH chemicals; many of these are also missing from the PubChemLite collection due to a lack of additional annotation content [241]. Of the 115,248 CIDs integrated in PubChem, 6275 CIDs come exclusively from the NORMAN-SLE (31 May 2022). This highlights that several NORMAN-SLE lists provide
valuable data that is not otherwise available in the open domain, including, e.g., mycotoxins that are not commercially available, but have been isolated via fungal fermentation and purification (S26 MYCOTOXINS [200]), as well as newly published PFAS and TPs added via the S46 PFASNTREV19 [46], S74 REFTPS [71] and S96 ECIPFAS [72] lists (among others).
An overview of the number of regulatory lists and major topics is given in Table 4. Key topics include pharmaceuticals, toxins, pesticides, PFAS, TPs, plastics, priority lists, surfactants, and suspect lists for water, with

Table 4 NORMAN-SLE lists (given by suspect list “S” number only for readability) associated with various topics and sources

Topic	Regulatory	Pharmaceuticals	Toxins	PFAS	TPs	Water	Pesticides	Nat. products	Plastics	Priority	Surfactants
Total Lists	16	11	11	10	10	9	7	7	6	5	4
Notes	S14, S17, S20, S23, S28, S30, S32, S36, S39, S47, S54, S63, S67, S86, S88, S97	S6, S10, S44, S45, S55, S56, S57, S58, S72, S76, S92	S24^, S26*, S29*, S37^, S40*, S43^, S52, S58, S64*, S75*, S85*	S9, S14, S25, S46, S80, S89, S92, S94, S95, S96	S8, S11, S38, S66, S68, S73, S74, S78, S79, S81	S2, S5, S36*, S39, S41, S63, S64, S82*, S84*	S11, S28, S59, S60, S69, S88, S94	S26, S29, S40, S59, S64, S75, S85	S20, S47, S48, S49, S67, S97	S15, S16, S36, S54, S63	S7, S8, S18, S23

Includes data from ECHA, EFSA, KEMI, REACH, UBA Excludes personal care products (S13) Includes *natural toxins, ^neurotoxins and others Includes *PMT lists
Plastics/chemicals associated with plastics Priority monitoring lists
PMT: persistent, mobile, toxic substances. Nat. products: natural products. Other abbreviations: see abbreviation listing
16 lists coming from European regulatory authorities. Future topics are discussed below.
Recognition, role and use of the NORMAN SLE The collection of download and view statistics on Zenodo, along with citation tracking, has helped track the impact of the NORMAN-SLE on the community, as shown in Tables 2 and 3. Since the Zenodo integration only commenced in 2019, these statistics only cover a fraction of the real-world use of the NORMAN-SLE. Several efforts known to the authors that build on NORMAN-SLE information are not captured within these statistics, including for instance CECSCREEN [84], which retrieved much of the NORMAN-SLE data that was integrated into CECSCREEN via CompTox. While a PubMed query on the NORMAN-SLE and the sub-collections was attempted to discover more citing articles, this did not return sufficiently reliable results for further interpretation (various text queries generated large numbers of false positives without finding true positives); it seems that environmental literature is not sufficiently covered in PubMed. Guidance is now provided on the NORMANSLE website to help
users correctly cite the works; it is hoped that this publication will also help to raise awareness of the resource for the wider scientific community— and will highlight the necessity to cite contributions, so that the level of community adoption becomes more visible over time.
The unique views, downloads, and citations available on Zenodo revealed some surprising results. While in NORMAN much focus was given to pesticides, pharmaceuticals, REACH registered chemicals and TP lists due to popular demand, the most popular list by far (see Table 3) proved to be S13 EUCOSMETICS [108], a collection of chemicals employed in cosmetics from EU regulations [106, 107]. The second most viewed list was a Swiss pesticide and metabolite list, S60 SWISSPEST19 [129], a quite recent collection by Kiefer et al. [128] from Eawag, which was expected to gain significant attention. This was an updated version of S11 SWISSPEST [189] from Moschet et al. [12]. While the NORMAN-SLE has several pharmaceuticals lists, the third most viewed list— a pharmaceuticals list, S72 NTUPHTW—was in fact a 2021 contribution from the National Taiwan University (Chen et al. [146]), which was received following a peerreview recommendation for submission to the NORMAN-SLE during manuscript revisions. This was the first such external contribution and marks a milestone in the NORMAN-SLE development. While S0 SUSDAT only appeared in 5th place according to views/downloads, these numbers are only a small fraction of the real statistics, since NORMAN SusDat is also available on a dedicated interactive website. This is also reflected in the relatively high citation count for SusDat compared with other lists. The NORMAN SusDat website (https://w
ww. norman-n etwork.c om/nds/s usdat/) was visited 120,221 times (20,258 times counting unique IP addresses per day) between 27 Feb. 2020 and 13 July 2022, compared with 26,318 visits to the NORMAN-SLE website (https:// www.n orman-network.com/n ds/SLE/). The original versions of two highly popular lists, the Food Contact Chemicals database (FCCdb) and the database of Chemicals associated with Plastic Packaging (CPPdb) are also available on Zenodo. These have much higher views and (for FCCdb only) download statistics associated with their original depositions compared with the NORMANSLE version (which directs viewers back to the original resource with a request to cite the original dataset). The numbers (10 July 2022) are (unique views/downloads): CPPdb [103] (2,082/659), S48/S49 CPPDBLISTA/B [104, 152] (594/1041), FCCdb [88] (8,612/3,703), S77 FCCDB [89] (410/398). Neither of these original depositions have

any citations. The reason for the parallel integration of these lists (i.e., an original version plus NORMAN-SLE version) is to ensure the maintenance of the full integration with the NORMAN-SLE website, PubChem and CompTox (as these require the preparation and archive of additional files, as well as the ability to edit the depositions and make any necessary adjustments).

All NORMAN-SLE lists feed into the merged collection NORMAN SusDat, which forms the basis of the NORMAN Database System (NDS) [29, 31] and integration into other NORMAN initiatives such as the Digital Sample Freezing Platform (DSFP) [266] and prioritization efforts (see Fig. 2). Several NORMAN-SLE lists are associated with NORMAN activities such as collaborative trials [4, 6] and NormaNEWS [184, 199]. NORMAN SusDat and the DSFP are used extensively in many studies in Europe (e.g., [142, 237, 240],), many of which are still in the process of being published. Beyond NORMAN activities and the statistics presented above, gauging the impact of the NORMAN-SLE remains rather intangible at present, since much of it also relates to the use of NORMAN SusDat. Anecdotally, the efforts behind the S11 SWISSPEST and S60 SWISSPEST19 lists have led to the inclusion of more compounds in the (Swiss) national monitoring program [267, 268], while the efforts related to S2 STOFFIDENT have resulted in the discovery of new P-containing
compounds (unpublished results).
FAIR data and chemical curation The decision to deposit the NORMAN-SLE collections on Zenodo helped "FAIRify" [22, 23, 269] the NORMAN-SLE via the provision of DOIs and versioning control. This helps trace updates and provide static URLs to data files, enabling powerful automatic integration such as that currently performed with PubChem (see Fig. 2), as well as providing the citation possibilities and statistics presented above. These are all features that are not currently possible via the infrastructure supporting the NORMAN-SLE website. Version control is important to track changes to the lists; not only in terms of fixing errors (i.e., curation), but also to keep historical records of lists as they change, since some chemicals that have, e.g., been phased out in the EU or changed in relevance may still occur in imported products and the environment. Overall, the data in the NORMAN-SLE is currently reasonably FAIR: Findable via the DOI and InChIKey for deep indexing; Accessible via the download options of
Zenodo; Interoperable via the use of SMILES and InChI; and Reusable via the open license (CC-BY 4.0) and the use of community standards where feasible, exemplified by the PubChem integration. A transition to the standardized templates proposed recently [24, 37, 270] will help FAIRify the NORMAN-SLE further; these templates
could also form the basis to help propose a set of chemical identifiers needed to establish unique (chemical) identifiers for the future European Open Data Platform.
While best efforts are made to map NORMAN-SLE contributions to identifiers correctly, the resources are not available for extensive curation efforts such as those performed by CompTox. This is coupled with the current "as is" philosophy, where lists are processed to best represent the data as provided. The versioning offered by Zenodo opens options for quality control and updating of lists, however this is still a very manual process and currently decoupled from updates to NORMAN SusDat— workflow and infrastructure upgrades to resolve this are underway. Since NORMAN-SLE lists are both sourced from and deposited to third party systems, and due to the different release cycles (PubChem updates daily, CompTox approximately annually), different versions of the data result—which can cause confusion. A coherent collaborative and timely process to update and circulate updated lists across the various systems would be beneficial; while this currently works well with the automated updates between PubChem and the NORMAN-SLE,
it is not yet possible with CompTox.
As mentioned above, the NORMAN-SLE hosts 99 suspect lists, which are then integrated into the merged NORMAN SusDat collection in the so-called "MS-ready" [263] form (ready for mass spectral screening). Access to "MS-ready" suspect lists [263] is urgently needed to reduce the number of trivial mistakes in suspect screening (such as searching for the exact masses of salts or polymers). However, the fact that many NORMAN-SLE lists contained both the original substances and their MSready form caused several problems with the PubChem integration and the subsequent mapping of structures to the expert knowledge contained within the lists (e.g., it is unclear to an automated method which structure is associated with the metadata: the original SMILES, or the MS-ready SMILES form). The integration of NORMAN-SLE content in PubChem and CompTox, along with discussions with developers, contributors and users is helping to develop better solutions to some of the challenges associated with the mapping of various chemical forms
over time.
Basic cheminformatics limitations still prevent the complete integration of suspect information, such as dealing with undefined structures for which no InChI or InChIKey exists (e.g., isomeric mixes such as surfactants, where several structures are hidden behind one detected "mass"). Taking examples from biocides, UVCBs of interest include: creosote; reaction products of 5,5-dimethylhydantoin, 5-ethyl-5-methylhydantoin with bromine and chlorine (DCDMH); reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1); or reaction

products of: glutamic acid and N-(C12-C14-alkyl)propylenediamine (Glucoprotamin). For those examples, mixture indicators or marker compounds associated with the UVCB may help evaluate these compounds. Biocidal polymers include "polyhexamethylene biguanide hydrochloride with a mean number-average molecular weight (Mn) of 1415 and a mean polydispersity (PDI) of 4.7 (PHMB(1415;4.7))" or "Polymer of formaldehyde and acrolein" or "Polymer of NMethylmethanamine (EINECS 204-697-4 with (chloromethyl) oxirane (EINECS 203439-8)/Polymeric quaternary ammonium chloride (PQ Polymer)", where pyrolysis GC–MS may assist analysis (not yet an explicit focus of the NORMAN-SLE lists). The CompTox team has made some efforts to address cases such as these through the definition of "related structures" and PubChem have released "concepts" to group several compounds related to substances under a given concept name, a topic that will be explored further at the upcoming BioHackathon [271]. The definition of chemical identifiers such as
an InChI(Key) describing UVCB substances is highly desirable to ensure that these efforts can be automated. While initial efforts such as the mixture InChI (MInChI) show promise (see e.g., Fig. 3 in [51]), there is room for further developments. Organometallic compounds (e.g., methylmercury compounds, organolead/organotin compounds, cyclic volatile methylsiloxanes, gadolinium compounds used as contrast agents) are cases that can be handled to an extent with the current approaches (although not in an "MS-ready" form). Upcoming InChI developments will hopefully improve the handling of organometallic species in databases in the near future [272]. Further examples related to biocides that are currently beyond the scope of the NORMAN-SLE (but are in part covered by the NDS) include microbial preparations or strains used as biocidal products, where metabarcoding or proteomics (peptide biomarkers) could be used for characterization, along with nanomaterials/nanoplastics.
Future updates: new submissions As described above, submissions and updates to the NORMAN-SLE were frozen during preparation of this manuscript. In the meantime, both new submissions and expressions of interest to update existing lists have been registered, partially stimulated by reaching out to all contributors during the writing of this work. Updates have been suggested for S17 KEMIMARKET [68], S28 EUBIOCIDES [196] with information from ECHA [273], S34 EXPOSOMEXPL [165, 166] with new data from [274] plus new microbial metabolites [275, 276] and S75 CyanoMetDB [118, 119] (next release due early 2023). Suggestions for new contributions include a list

of endocrine disruptors within the activities of PARC, the Proposition 65 (Prop-65) list of chemicals from the California EPA [277], Phenol-Explorer [278–280], the Database on Migrating and Extractable Food Contact Chemicals (FCCmigex) [281], and finally a shale gas suspect list [282] that has been applied in other studies: [283, 284] and will fill a long-identified gap with respect to fracking-related content.
Beyond these new suggested submissions, future developments involve improving the current submission system to the NORMAN-SLE. The current submissions generally rely on personal contacts, with only one submission recommended externally so far (S72 NTUPHTW [147]). Manual work for the NORMAN-SLE team would be reduced if contributors would consider using a template, as described recently [24, 37, 270]. While the evolution of openly available batch services offered by PubChem [40] and CompTox [41] have greatly eased the mapping of contributed lists to include the required information for upload, a further semi-automation of this workflow would ease matters further and is already in planning. However, extensive curation based on CAS as performed by CompTox is currently out of scope of the NORMAN-SLE, which is based on fully open access resources. While a feedback loop between CompTox and the NORMAN-SLE would help the NORMAN-SLE benefit from the CompTox curation, this is not currently possible. A submission system such
as that offered by PubChem could be considered in the future, but is currently beyond reach of the resources available for the NORMAN-SLE. While these enhancements would be desirable, overall the current system has held up well for 99 lists so far and more contributions are welcomed by emailing the NORMAN-SLE team as detailed on the website: https://w ww.n orman-network.com/n ds/SLE/.
Future updates: potential new features Beyond the new submissions and processing updates mentioned in the previous section, several new features have been suggested (and are being considered) for the NORMAN-SLE and/or the broader NORMAN Database System. These can be grouped into four major areas reflected in the following paragraphs: experimental, TPs, categorization/use and regulatory.
On the experimental side, additional functionality to account for physical chemical properties such as mass, polarity, likely ionization mode and amenability to either GC or LC would be beneficial, along with the link to available MS/MS data and/or reference standards for further confirmation. This information is included to a large extent in NORMAN SusDat, which provides a centralized access point for this information, along with predicted toxicity values [264] and retention indices [238],

but will be streamlined and automated further, also to account for possibilities arising from the PubChem integration. Documentation on how to obtain some of this information via PubChem is also available, e.g., for MS/ MS [252] and CCS values [253–255]. Advanced Entrez queries (via PubChem) can be used to limit this to certain measurement modes. Another suggested enhancement related to UVCBs would be to include important substructures such as the head group of surfactants or repeating unit of polymers, which could be linked to MS/ MS fragments.
A large focus has been placed on TPs over the recent years. A continuation of ongoing efforts will include adding more TPs, including the extraction of data from literature to fill data gaps [71, 174, 205] and the integration of workflows in patRoon [257] in a manner compatible with other NTS workflows. Over the years, there has been increasing interest to add lists of predicted TPs to the NORMAN-SLE, with submissions including predicted TPs for S6 ITNANTIBIOTICS [159], S71 CECSCREEN [85] (both generated with BioTransformer [111]) and S38 SOLNSLMCTPS [102]. While such lists are valuable for researchers performing NTS, these can cause problems with downstream integration with the NDS, CompTox and PubChem as these predicted structures are not necessarily observed and verified, while the number of entries can be an order of magnitude higher (or more) than the source list. These datasets are generally decoupled from the cross-integration at present. A future discussion for NORMAN will be how best to integrate predicted
TP data, with the possibility of a “Transformations” module to be added—potentially to represent both documented transformations (e.g., similarly as shown in the insets in Figs. 2 and 5) and predicted transformations.
As the NORMAN-SLE list numbers climb, and with several contributions covering related topics (see Table 4), further refinements will be needed to group lists together and allow the selection of certain subsets for different use cases, or the sorting of lists by categories. The extensive integration with PubChem and the resulting need for organization of NORMAN-SLE content in both CompTox and PubChem has given rise to categorization and classification efforts, and preliminary functionality allowing this is already integrated into NORMAN SusDat. Since there is great interest in the gathering of “Use” information and categorization in general, NORMAN has already initiated activities within the Prioritization working group [285] to define and collect relevant use information and categories from members. These activities will feed into subsequent future developments within NORMAN, PARC [28, 29], EU projects such as ZeroPM [229] and beyond.
The NORMAN-SLE is a community resource built on an incredible amount of volunteer effort and rather limited financial resources. The entire NDS is supported through the NORMAN Association and project funding obtained by individual contributors. The integration with external resources such as PubChem, CompTox and Zenodo provides significant added value beyond the capabilities available to NORMAN. This approach is key to foster cooperation among existing regulatory frameworks, helping to share data and improve chemical risk assessment in the shift towards a “one substance, one assessment” paradigm [286]. With the EU strongly supporting Open and FAIR data, including large initiatives such as PARC [28, 29] and EIRENE [30], along with Green Deal projects such as ZeroPM [229], opportunities for further developments, consolidation and harmonization with broader EU efforts, including the future Open Data Platform appear promising. While the idea behind the NORMAN-SLE has broad support, the current infrastructure and personnel
could not currently support, for instance, a requirement to host and thus make all European environmental research data Open and FAIR. If, however, the experiences in building the NORMAN-SLE could help contribute towards establishing such a platform (to which the NORMAN-SLE could contribute), this would be a huge benefit for research and researchers.
Conclusions The NORMAN Suspect List Exchange (NORMAN-SLE) was created to provide a service to NORMAN members and the greater scientific community, in response to a clear need identified in the NORMAN Non-target Collaborative Screening Trial [4]. Through the provision of a centralized website to collect various suspect lists and references, information exchange is ensured to apply the “screen smart” strategy on specific scientific questions. This FAIRified resource is archived on Zenodo to give DOIs for each set, allowing the cross-integration with other resources and formal citation of datasets, raising the profile of the research of various contributors. The combined list formed from all NORMAN-SLE contributions, NORMAN SusDat, serves as a basis for chemical management for the entire NORMAN Database System (NDS), including the NORMAN Digital Sample Freezing Platform (DSFP) [266].
The NORMAN-SLE is not intended to replace major open compound databases such as ChemSpider, PubChem or CompTox, but rather offers a specialized, complementary service targeted to the environmental science community, particularly in relation to suspect screening, for integration within these larger resources, as done with CompTox and PubChem. Raising the awareness about relevant suspect screening lists and the

quality issues surrounding suspect screening is vital for improving the identification of contaminants of emerging concern in the environment, biota, and products, thereby helping to reduce the number of molecular unknowns in mass spectrometry analyses and to facilitate more comprehensive chemicals assessments. The NORMAN-SLE welcomes new submissions of suspect lists within the scope, along with other ideas and feedback, as described on the NORMAN-SLE website (https://www.norman- networ k.com/n ds/S LE/).

Abbreviations ASNT: Abstract Syntax Notation (ASN.1) Text format; ATC: Anatomical Thera peutic Chemical code; CAS: Chemical Abstract Service; CCS: Collision cross section (ion mobility experiments); CDK: Chemistry Development Kit; CECs: Contaminants of Emerging Concern; CID: PubChem Compound Identifier; CPPdb: Chemicals associated with Plastic Packaging database; CSID: Chem Spider Identifier; CSV: Comma Separated Values; DOI: Digital Object Identifier; DSFP: Digital Sample Freezing Platform; DSSTox: Distributed Structure-Search able Toxicity (database); DTXSID: Distributed Structure-Searchable Toxicity (DSSTox) substance identifier; EC: European Commission; ECHA: European Chemicals Agency; ECI: Environmental Cheminformatics group, University of Luxembourg; EFSA: European Food Safety Authority; EIRENE: Environmental Exposure Assessment Research Infrastructure; EU: European Union; FAIR: Findable, Accessible, Interoperable, Reusable; FCCdb: Food Contact Chemicals database; FCCmigex: Database on Migrating and
Extractable Food Contact Chemicals; GC: Gas chromatography; HRMS: High resolution mass spectrom etry; InChI: International Chemical Identifier; InChIKey: Hashed form of the International Chemical Identifier; IP: Internet Protocol; JRC: Joint Research Centre; JSON: JavaScript Object Notation; KEMI: Swedish Chemicals Agency; LC: Liquid chromatography; MInChI: Mixture InChI; MS: Mass spectrometry; MS/MS: Tandem mass spectrometry; NDS: NORMAN Database System; NMR: Nuclear magnetic resonance; NORMAN: Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances; NORMAN SusDat: NORMAN Substance Database; NORMAN-SLE: NORMAN Suspect List Exchange; NTS: Non-Target screening; PARC: European Partnership for Chemicals Risk Assessment; PFAS: Per- and polyfluoroalkyl substances; PMT: Persistent, mobile and toxic substances; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals (EU regulation); SDF: Structure Data Format; SEO: Search
Engine Optimiza tion; SID: PubChem Substance Identifier; SMILES: Simplified Molecular-Input Line-Entry System; TPs: Transformation products; UBA: German Environment Agency (Umweltbundesamt); US EPA: United States Environmental Protection Agency; UVCBs: Substances of Unknown or Variable Composition, Complex Reaction Products or Biological Materials; XML: Extensible Markup Language; ZeroPM: Zero Pollution of Persistent, Mobile Substances (EU project).

Supplementary Information

The online version contains supplementary material available at https://d oi. org/1 0.1 186/s12302-022-00680-6.

Additional file 1: Summary of the NORMAN-SLE datasets (CSV format) as of 4 May 2022 [81].

Additional file 2: Overview of the NORMAN-SLE website (DOCX format) as of 30 May 2022 [82].

Additional file 3: Summary of Zenodo view and download statistics, plus citations (CSV format) as of 28 April 2022 [235].

Additional file 4: Summary of Zenodo citations plus DOIs per list (CSV format) as of 1 May 2022 [236].

Additional file 5: Authorship contributions and acknowledgements mapped to NORMAN-SLE lists (XLSX format).

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Availability of data and materials All data integrated in the NORMAN Suspect List Exchange are available from the NORMAN-SLE website (https://www.n orman-networ k.com/n ds/S LE/) and on the Zenodo NORMAN-SLE community website (https://z enodo.o rg/ commun ities/n orman-sle) or via the individual DOIs (see Table 1). The merged NORMAN SusDat collection is also available (https://www.norman-networ k. com/nds/susdat/). Individual lists can be accessed by their code on CompTox, the collection can be found under this search URL (https://comptox.epa.g ov/ dashbo ard/chemic al-lists?search=N ORMAN) or on the NORMAN-SLE website (https://www.n orman-network.c om/nds/S LE/). The NORMAN-SLE is available as data source in PubChem (https://p ubche m.n cbi.nlm.nih.g ov/source/2 3819) and browsable as a classification tree (https://pubche m.n cbi.n lm.nih.gov/ classi fication/#hid=1 01). Detailed annotation content is available in several PubChem compound records, with
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Wide-scope target screening characterization of legacy and emerging contaminants in the Danube River Basin by liquid and gas chromatography coupled with high-resolution mass spectrometry ☆
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ABSTRACT
A state-of-the-art wide-scope target screening of 2,362 chemicals and their transformation products (TPs) was performed in samples collected within the Joint Danube Survey 4 (JDS4) performed in 2019. The analysed contaminants of emerging concern (CECs) included three major categories: plant protection products (PPPs), industrial chemicals and pharmaceuticals and personal care products (PPCPs). In total, 586 CECs were detected in the samples including 158 PPPs, 71 industrial chemicals, 348 PPCPs, and 9 other chemicals. A wide-variety of sample matrices were collected including influent and effluent wastewater, groundwater, river water, sediment and biota. Forty-five CECs (19 PPPs, 8 industrial chemicals, 18 PPCPs) were detected at levels above their ecotoxicological thresholds (lowest predicted no-effect concentration (PNEC) values) in one or more of the investigated environmental compartments, indicating potential adverse effects on the impacted ecosystems. Among them 12 are legacy substances; 33 are emerging
and qualify as potential Danube River Basin Specific Pollutants (RBSPs). Moreover, the efficiency of the wastewater treatment plants (WWTPs) was evaluated using 20 selected performance indicator chemicals. WWTPs showed effective removal (removal rate ≥80%) and me- dium removal (removal rate 25–80%) for 6 and 8 of the indicator chemicals, respectively. However, numerous contaminants passed the WWTPs with a lower removal rate. Further investigation on performance of WWTPs is suggested at catchment level to improve their removal efficiency. WWTP effluents are proven to be one of the major sources of contaminants in the Danube River Basin (DRB). Other sources include sewage discharges, in- dustrial and agricultural activities. Continuous monitoring of the detected CECs is suggested to ensure water quality of the studied area.
1. Introduction
Being the second largest catchment region in Europe, the Danube River Basin (DRB) serves over 80 million people by providing drinking water, industrial and agricultural water supply, hydroelectric power generation, tourism and fisheries among others (Alygizakis et al., 2019). Anthropogenic activities constantly introduce contaminants of emerging concern (CECs) into the DRB, such as pharmaceuticals and personal care
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Fig. 1. Spatial[«2654]distribution of the environmental samples collected within the JDS4. Interactive map is available online at https://norman-data.eu/JDS4_Samples.
products (PPCPs) from domestic wastewater (Skrbic et al., 2018) and plant protection products (PPPs) from agricultural activities (Gaspar- otti, 2014). Industrial production could introduce industrial chemicals and PPCPs to the environment. All these chemicals are released to various environmental compartments at alarming levels across the globe (Thompson and Darwish, 2019). It is therefore essential to monitor the water quality of the DRB. The Joint Danube Survey (JDS) was conducted in 2001, 2007, 2013, and 2019 to collect data for water quality evalu- ation on the DRB and its major tributaries. The present study outlines some chemical findings from the Joint Danube Survey 4 (JDS4) per- formed in 2019.

PPPs, industrial chemicals, and PPCPs were selected for this study as these compounds could pose threats to the ecosystems and human via bioaccumulation or mobility. Depending on their physico-chemical properties, some of them tend to bioaccumulate in living organisms and could reach human and various organisms via the food chain (Al-Farsi et al., 2017; Kalyabina et al., 2021). Some PPPs and industrial chemicals, such as certain per-and polyfluoroalkyl substances (PFASs) could cause adverse reproductive and developmental effects in mam- mals and vertebrates (Blake and Fenton, 2020); and pesticides could reduce biodiversity by adversely affecting survival and reproduction of non-target species (Geiger et al., 2010). In addition, some studied con- taminants have mobile properties and could end up in groundwaters used for production of drinking water (Kampouris et al., 2022). Waste- water treatment plant (WWTP) effluent plays a key role in chemical pollution (including PPCPs, industrial chemicals and PPPs) of surface
waters used as drinking water sources (Troger et al., 2020). Some PPCPs are included in the EU watch list (Commission Implementing Decision 2022), however, the regular monitoring of most PPCPs is not requested by the current EU legislations despite their ubiquitous presence. Comprehensive occurrence data are required to support the future reg- ulatory monitoring at the EU and basin scale.
The selected CECs are constantly emitted from various sources including anthropogenic activities and WWTP effluent discharge (Muller et al., 2002). Some CECs were found to pass the WWTPs unal- tered (partially or fully), and are being continuously introduced into the DRB (Alygizakis et al., 2019). WWTP effluents have been proven to be a major point source of PPCPs in the aquatic ecosystems (Ebele et al., 2017). Some CECs found in effluent wastewater are persistent and barely undergo transformation in WWTPs, such as perfluorooctane sulfonic acid (PFOS) (Thompson et al., 2022). These substances from WWTPs could also biomagnify in the food chain or enter groundwaters regarding their mobility (Aristi et al., 2015; Zhen et al., 2018). It is therefore essential to evaluate the removal efficiency of WWTPs and characterize the CECs emitted by the plants.
Many reference laboratories collaborated to identify a wide spectrum of CECs in the DRB. This study reports the findings of four analytical laboratories: the Environmental Institute (EI, Slovakia), the Bavarian Environmental Agency (LfU, Germany), the Joint Research Centre (JRC, Italy) and the University of Athens (UoA, Greece). The laboratories are equipped with analytical methods and state-of-the-art analytical instrumentation to perform multi-residue target screening of the 2,362 analytes of interest (full list available in the supplementary material). Chemical screening involved both legacy compounds and emerging contaminants. The aims of this study were to (1) address the fate of a broad range of CECs and their TPs in the DRB, (2) identify CECs that are emitted by the WWTPs in the DRB, (3) evaluate the removal efficiency of the WWTPs using a set of selected indicator chemicals (substances proposed by Water Europe, NORMAN Association and Swiss legislation) (Joint Norman and Water Europe Position Paper: Contaminants
of Emerging Concern in Urban Wastewater, 2019), and (4) propose DRB specific pollutants.

2. Materials and methods

2.1. Investigated samples and data collection

The study covered 106 environmental samples including 11 influent wastewater, 11 effluent wastewater, 51 river water, 7 groundwater, 22 biota and 4 sediment samples, all obtained within the JDS4 organized by the International Commission for the Protection of the Danube River (ICPDR) in June and July 2019 (Fig. 1). 24h flow-proportional com- posite influent and effluent wastewater samples were collected with certified clean polycarbonate bottles under normal WWTP operating conditions (Liˇska et al., 2021).
The determination of all studied chemicals was collected in the preprogrammed spreadsheets termed ‘Data Collection Templates’ (DCTs). These spreadsheets gathered all necessary metadata (e.g., sampling site name, date, coordinates, sample matrix etc.) and information (e.g. limit of detection and quantification (LOD & LOQ), validation levels of the adopted methods and accreditation of the laboratory etc.) for quality evaluation of the results. The DCTs are available on the NORMAN Database System and its EMPODAT module (Norman: Norman Empodat Database - Chemical Occurrence Data, 2022). When a contaminant was detected above its LOD and below its LOQ, the LOQ/2 value would be considered as the detected concentration level for reporting purposes, as suggested by Directive 2009/90/EC (The Commission of the European Communities, T. 2009).

2.2. Sample preparation and instrumental analysis

Some compounds among the studied CECs were analyzed by more than one laboratory, as shown in the “Screened compounds” tab of the supplementary material. For compounds detected by multiple labora- tories, the result was selected in the order of (a) the laboratory accredited for the analysis of the substance; (b) the laboratory which performed the analysis of the substance with internal standard; (c) the highest measured concentration. A group of 69 polar and hydrophobic compounds was analyzed by the JRC, including Water Framework Directive (WFD) priority substances, Watch List compounds and Danube River Basin Specific Pollutants (RBSPs) identified within JDS3 (Brack, 2019; Liˇska et al., 2015). A large volume solid phase extraction (LVSPE) device (MARIANI-Box (Mariani et al., 2017)) was adopted to obtain and extract effluent wastewater, river water and groundwater samples. The samples were filtered (7 L for groundwater, 5 L for river water and 0.5 L for wastewater), and spiked with a mix of stable isotope labelled
internal standards. Subsequently, solid phase extraction (SPE) (J2 Scientific) was performed on an Atlantic HLB-H SPE Disk (Horizont Technology) mounted in the MARIANI-Box. Prior to analysis, the extracts were evaporated under a gentle nitrogen stream. Details of the extraction process can be found elsewhere (Mariani et al., 2020). Gas chromatography/high-resolution mass spectrometry (GC-HRMS) (DFS, Thermo) and liquid chromatography/tandem mass spectrometry (LC-MS/MS) (QTrap 5500, Sciex) were utilized for the determination of non-polar and polar compounds, respectively (Mariani et al., 2017).
A group of 141 pesticides and their TPs was analyzed by LfU. River water and groundwater samples underwent an on-line SPE using C18 material combined with liquid chromatography/high-resolution mass spectrometry (LC-HRMS) (QExactive, Thermo). A Zorbax Eclipse plus C18 column (Agilent) with dimensions 3.5 µm, 2.1×150 mm was used. Details of the analytical method are included in the “LC-HRMS method” tab of the supplementary material.

A group of 2,290 CECs and their TPs was analyzed in wastewater, river water and groundwater samples. Samples were extracted in the laboratory of the EI following an automated extraction program (Aly- gizakis et al., 2020). Samples underwent SPE with a HORIZON SPE-DEX 4790 device (USA), then concentrated on Atlantic HLB-M Disk with 47 mm disk holder. The extracts were evaporated under a gentle stream of nitrogen and reconstituted in 50:50 methanol:water (500 uL total vol- ume extract). Samples' extracts were shipped to the UoA for further analysis. The treatment and extraction of sediment samples following a validated protocol (Gago-Ferrero et al., 2015), treatment and extraction of biota samples using a multi-residue optimized method for fish tissues (Dasenaki and Thomaidis, 2015) were both performed at the UoA. Two complementary instrumental methods were used for the screening of targeted CECs and their TPs in the samples' extracts. Extracted samples were analyzed for targeted compounds by an in-house UHPLC-ESI-QTOF
method (Gago-Ferrero et al., 2020), of which full-scan MS and MS/MS acquisition were adopted. Dionex UltiMate 3000 RSLC (Thermo Fisher Scientific) coupled to a Maxis Impact QTOF (Bruker) was utilized for the analysis. Moreover, a highly sensitive LC-MS/MS method using multiple reaction monitoring scan mode was utilized for the determination of 158 commonly consumed pharmaceuticals, antibiotics, illicit drugs, drugs of abuse and their TPs at trace levels (Alygizakis et al., 2016). The specific and more sensitive LC-MS/MS method was used to detect specific contaminants occurring at low concentration levels. The high-resolution mass spectrometry analytical method is less sensitive but provides information for a broad range of contaminants.

2.3. Quality assurance and quality control

A thorough quality assurance and quality control (QA/QC) program was applied in the sample preparation procedures and instrumental analysis methods. Prior to extraction, a mix of internal standards was added into each sample. The generic sample preparation protocols that
Fig. 2. Removal rates of indicator chemicals from the studied 11 WWTPs in the DRB.
were used assure satisfactory recovery (typically above 60%) for the majority of the targeted compounds. Moreover, six additional blank samples were used for quality control. The blank samples were prepared and examined together with the samples. This process checks for any external contamination which could be introduced during the sampling campaign, sample preparation of the extracts and analytical procedures. The field blank samples were MilliQ water brought to the field and extracted at the laboratory together with the real samples. The signals observed in blank samples were subtracted from the signals observed in real samples. The QA/QC program and logistic planning of the sampling process are thoroughly described in the JDS4 Scientific Report (Li˘ska et al., 2021).

A collaborative trial on the three screening methods applied (by JRC, LfU, and UoA) was performed. The performance of the methods on all 10 compounds commonly analyzed by the laboratories (acetamiprid, atrazine, desethylterbutylazine, dimethenamid, imidacloprid, metaza- chlor, metolachlor, simazine, tebuconazole, terbutryn) was compared in terms of limits of quantification (LOQs), detection frequencies, and consistency with each other, as shown in the "Comparison of methods" tab of the supplementary material. In general, the JRC method showed better sensitivity as compared to the SPE-based screening methods as more concentrated extracts were analyzed, difference in LOQs for over an order of magnitude for some compounds (atrazine, imidacloprid, metolachlor, etc.) was observed. Thus, higher sensitivity resulted in higher number of detections by the JRC method. Nonetheless, deter- mined concentrations of the 10 compounds by all methods showed a good agreement in most cases (within a factor of 3).

2.4. Evaluation on removal efficiency of WWTPs using indicator substances

For the systematic assessment on the performance of WWTPs in the wastewater abatement process, a set of 20 compounds was selected as performance indicators based on the following criteria: (1) are of high consumption and regularly found in WWTP influents, (2) occur in most effluent of WWTPs at detectable levels, (3) are easily and routinely measured by as few as possible analytical methods (optimally one method), (4) cover a broad range of physico-chemical properties and biodegradability, which affects their removal rate at various treatment processes, (5) undergo a similar degree of abatement in advanced treatment technologies (e.g., ozonation or sorption to activated carbon (AC)), and (6) are representative of a broad range of treatability fea- tures; from "biodegradable during conventional activated sludge

treatment or biofiltration", to "not degradable during conventional activated sludge treatment or biofiltration, but amenable to chemical oxidation or sorption to AC", and "not degradable during conventional activated sludge treatment or biofiltration, and not amenable to chem- ical oxidation or sorption to AC".

The 20 compounds and their abatement rate are included in Fig. 2. The efficiency of WWTPs was evaluated by its removal rate of the 20 performance indicators. It should be noted that efficient removal of WWTP relates to a reduction in the concentration of a contaminant by 80% or above, instead of complete removal of the substance. This fol- lows the Waters Protection Ordinance of the Swiss Federal Council which included 80% abatement as the target for the reduction of CECs in WWTP (The Swiss Federal Council: 2018).

2.5. Risk assessment

To assess the risk of the detected substances, the concentrations of the contaminants were evaluated in relation to the respective predicted no-effect concentration (PNEC) values. The occurrence of CECs with detected levels above PNEC were considered to represent a potential risk for the impacted ecosystem. PNEC values for all detected substances were extracted from the NORMAN Ecotoxicology Database (Norman: Norman Ecotoxicology Database, 2023) (a part of the NORMAN Data- base System Dulio, 2020). For compounds where no experimental toxicity data was available, PNECs were derived by QSAR models (Aalizadeh et al., 2017). For risk assessment purposes, the lowest PNEC was selected in the order of (a) environmental quality standard (EQS) values; (b) experimental PNEC values from reference laboratories; (c) in-silico predicted PNEC. Steroids in biota were considered as naturally occurring compounds and were not considered for the risk assessment.

3. Results and discussion

Category, contributor, NORMAN ID, LOD, LOQ, PNEC at various studied matrix, matrix specific frequency of appearance (FoA) of, min- imum and maximum detected concentrations for the 586 detected CECs are included in the "Detected compounds" tab of the supplementary material. Among them are 158 PPPs, 71 industrial chemicals, 348 PPCPs, and 9 other chemicals. Sections 3.1–3.5 include the discussion of results by environmental matrix; Sections 3.6 and 3.7 include the dis- cussion of CECs of concern (by the distribution across environmental matrices (3.6) or by environmental risk assessment (3.7)).

3.1. River water

In total, 142 PPCPs and their TPs were detected in JDS4 river water samples. Caffeine, metformin, sulfamethoxazole, sucralose, clari- thromycin, 19-norandrosterone, carbamazepine and its metabolite carbamazepine-10,11-dihydro-10,11-dihydroxy were detected in all 51 river water samples (100% FoA). Meanwhile, 59 PPCPs (42%) showed <10% FoA. Most of the PPCPs were detected at levels up to tens of ng L− 1, exceptions include 19-norandrosterone with maximum concentra- tion of 1171 ng L− 1 (highest among determined PPCPs). Attention was drawn to six detected PPCPs that were listed in the EU Watch List (EU 2022/1307) (Commission Implementing Decision, 2022), including amoxicillin, ciprofloxacin, sulfamethoxazole, trimethoprim, venlafaxine and fluconazole. The 6 legacy substances occur at low concentration levels and no PNEC exceedance was observed. Nonetheless, high FoA (84% and 100%) were observed for amoxicillin and sulfamethoxazole, and therefore further emission should be strictly controlled.

Among the 40 industrial chemicals determined in river water sam- ples, high FoA was also observed in river water for six PFASs: per- fluorooctanoic acid (PFOA, FoA 100%), perfluorooctanesulfonic acid (PFOS, FoA 96.1%), perfluorohexanoic acid (PFHxA, FoA 94.1%), per- fluorohexanesulfonic acid (PFHxS, FoA 90.2%), per- fluorobutanesulfonic acid (PFBS, FoA 86.3%) and perfluoroheptanoic

acid (PFHpA, FoA 56.9%). They were generally detected at low average concentration levels ranged from 0.6 ng L− 1 (PFBS) to 3.2 ng L− 1 (PFHxA). Nevertheless, their ubiquitous presence in river water is of concern as some of them possess a high bioaccumulation potential (Haukas et al., 2007). WWTP effluent discharge was found to be a common point source of PFASs as a result of inefficient removal of PFASs at WWTPs (Phong Vo et al., 2020).

Another important sub-class of industrial chemicals detected was phenols, including 2,4-dinitrophenol (FoA 100%, average concentration 3.6 ng L− 1) and 4-tert-octylphenol (4-t-OP, FoA 88.2%, average con- centration 55.2 ng L− 1). The latter one is a priority substance under the WFD (ECHA Substance Infocard - 4-(1,1,3,3-tetramethylbutyl)phenol, 2021). Four novel bisphenol A (BPA) related compounds were also detected: bisphenol A diglycidyl ether, bisphenol A (3-chloro-2-hy- droxypropyl) glycidyl ether, bisphenol A (2,3-dihydroxypropyl) glycidyl ether, and bisphenol A bis(3-chloro-2-hydroxypropyl) ether. These BPA related compounds were detected only in the Upper Danube (Germany, Austria, and Slovakia) at levels up to 535.8 ng L− 1 (BPA bis (3-chloro-2-hydroxypropyl) ether in JDS4-4 (Germany)), which in- dicates the presence of contamination sources of BPA in the Upper Danube. This could be a warning signal as BPA is well known for its toxic, mutagenic and carcinogenic effects in living organisms (Micha- lowicz,

2014), and BPA analogues could cause endocrine effects in aquatic species (Liu et al., 2021). These compounds are of regulatory interest, especially the prioritized phenols and BPA related compounds shown in Section 3.7.

Among the 119 PPPs detected in river water samples, 28 showed high FoA (>80%). Majority of the determined PPP concentrations were below 10 ng L− 1. There were exceptions including metolachlor and its TP metolachlor-ESA: both compounds showed 100% FoA with average concentrations of 24 and 42 ng L− 1, respectively. Carbendazim was detected with a FoA of 92% and an average concentration of 151 ng L− 1, which has been banned in the EU since 2019 (European Commission: Commission Implementing Decision (EU), 2019), with exception on some biocidal products (European Commission: Commission Imple- menting Decision (EU), 2021).

3.2. Groundwater (GW)

In total, 124 of the 2362 targeted compounds were detected in the seven GW samples. The results from each GW sample were compared with the results from the closest river water sample (1 – 41 km apart from the GW site) to identify potential source of contaminants. Half of the detections were attributed to a monitoring pair (a GW sample and the corresponding river water sample of highest proximity). The detected compounds were mainly PPCPs, PPPs and industrial chemicals. Such common presence of the detected CECs suggests river water as a potential contamination source, which is commonly observed for com- pounds of high mobility (see Section 3.6). For the other sites and com- pounds, local or regional activities could be the source of contamination. The identification of contamination source is important for pollution control of GW of the DRB.

In sum, 48 PPPs and their TPs were determined in the seven GW samples. The highest cumulative concentration of PPPs was observed at the GW site in Romania (140 ng L− 1); the highest individual PPP con- centration was observed at the same site for metolachlor-ESA (38 ng L− 1). No exceedance of the quality standards under the EU Groundwater Directive was observed (100 ng L− 1 and 500 ng L− 1 for individual and total concentrations of pesticide substances and relevant metabolites, respectively (European Parliament: Directive, 2006). The same para- metric values were listed under the EU Drinking Water Directive as maximum permissible values (The Council of the European Union, E., 1998). However, further pollution should be strictly controlled.

A total of 48 PPCPs were detected in the studied GW sites. The highest cumulative concentration was observed at the GW site in Croatia (650 ng L− 1), the site also showed the highest individual PPCP

concentration of 520 ng L− 1 for the antiepileptics vigabatrin. This is above the group total quality standard for pharmaceuticals of 500 ng L− 1 as suggested in Annex I of Groundwater Directive (2006/118/EC), which is under discussion to bring the quality standard to a lower con- centration (Scientific Committee on Health, 2022). No exceedance of the quality standard was observed in other GW sites. Seven antibiotics were detected in the GW samples, with up to 3 antibiotics (Bulgarian GW site) in each sample. The highest cumulative concentration of antibiotics was observed at the Hungarian GW site (25 ng L− 1), the site also showed the highest individual antibiotic concentration of 23 ng L− 1 for sulfameth- oxazole, which is listed in the EU Watch List (EU 2022/1307) (Com- mission Implementing Decision, 2022). Nonetheless, the detected concentration is well below the groundwater quality standard of 100 ng L− 1 (Scientific Committee on Health, 2022).

In total, 28 industrial chemicals were determined in the seven GW sites, including phosphate flame retardants, PFASs, benzotriazoles and benzothiazoles, phenolic substances, and other industrial chemicals. The number of industrial chemicals observed per GW-site ranges from 4 to 13; and the cumulative concentration per GW-site ranges from 320 to 720 ng L− 1. Four PFASs were each determined in GW samples at low concentrations ranging between 0.5 and 18 ng L− 1, including PFOS (3 GW-sites), PFHxA (4 GW-sites), PFOA and PFBuS (5 GW-sites each). No exceedance of the quality standards proposed by EU Drinking Water Directive was observed in the seven GW sites (100 ng L− 1 for the sum of a list of selected 20 PFASs and 500 ng L− 1 for total PFAS level (European Parliament: Directive (EU), 2020). It should be noted that bisphenol A was determined at all seven GW-sites at concentration between 93 (GW site in Croatia) and 159 ng L− 1 (GW site in Romania), which is well above the quality standard for bisphenol A of 10 ng

L− 1 that is under discussion for inclusion in the EU Drinking Water Directive (European Parliament: Directive (EU), 2020). Bisphenol A was not detected in river water samples which indicates other contamination sources to the GW in the DRB. This finding is alarming and is indicative of regulatory moni- toring of these industrial chemicals in GW of the DRB.

Some of the detected CECs could act as endocrine disruptors by interfering with the hormone systems, such as bisphenol A and PFOA (Liu et al., 2021; Chaparro-Ortega et al., 2018). The occurrence of such compounds (despite the levels below respective quality standards or permissible values) is of concern, as they could reach human via drinking water produced from GW, and accumulate in human body. Moreover, the presence of the 7 antibiotics in the GW of DRB is also of concern, as the continuous human exposure of antibiotics could intro- duce antibiotic resistance and potentially public health issues (Kam- pouris et al., 2022). The investigation on the emission source of such compounds is essential to maintain the quality of GW of the DRB, which provides drinking water to millions of people (Alygizakis et al., 2019).

3.3. River sediments

Overall, 31 PPCPs and their TPs were detected in the four analyzed samples. Antibiotics was the most frequently detected class of com- pounds (10), followed by antidepressants and antipsychotic drugs (7). Clinical waste from hospitals is therefore worth investigating as a po- tential contamination source of such PPCPs. Most of the detected PPCPs were determined at levels up to tens of μg kg− 1 dry weight. The most abundant PPCPs found were apophedrin (maximum concentration of 213 μg kg− 1 in JDS4-6 (Germany)), the UV-filter octocrylene (maximum concentration of 162 μg kg− 1 in JDS4-47 (Bulgaria)) and the antibiotic sulfadiazine (maximum concentration of 120 μg kg− 1 in JDS4-47 (Bulgaria)). Eight out of the 31 PPCPs and TPs were detected in all four sediments samples (FoA 100%), including triethylcitrate, ami- sulpride, citalopram, bisoprolol, apophedrin, methocarbamol and gal- axolidone. Most PPCPs could have entered river sediment from the aquatic environment via the process of sedimentation after adsorption
to suspended particulate matter (Vieno et al., 2005).

In total, 19 industrial chemicals were detected in the sediment
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samples. Surfactants was the dominant category of industrial chemicals found in river sediments (n = 12): diglyme, benzododecinium, dide- cyldimethylammonium and triglyme with FoA of 100% and laur- yldiethanolamide, tetraethyleneglycol-monododecyl ether, N,Ndimethyltetradecylamine, N,N-dimethyltetradecylamine-N-oxide, N,Ndimethyldodecylamine, N-Methyldodecylamine, tributylamine with FoA≥ 50%. The most abundant industrial chemical found was the phthalate DEHP, with maximum detected concentration of 1342 μg Kg− 1 in JDS4-24 (Hungary). This finding is of high concern as DEHP is a WFD priority substance and is toxic to reproduction and endocrine disrupting (ECHA Substance Infocard - Bis(2-ethylhexyl) phthalate, 2022). Inves- tigation on the emission source of such threatening compound at the region near the sampling site by the local authority is important to stop further pollution.

River sediments were less contaminated by PPPs in comparison with other investigated matrices, only 8 PPPs were determined in the sedi- ment samples. The most frequently detected PPPs was carboxin, which was detected in all 4 sediment samples (FoA 100%) with an average concentration 10 μg Kg− 1. It was followed by the pesticide barban with 75% FoA and average concentration 67 μg Kg− 1. Three PPPs (oxfenda- zole, aramite and desisopropyl-atrazine) were detected at concentration levels below the respective limits of quantification (LOQ). The other 3 PPPs (methiocarb, cadusafos and chlordimeform) were detected at concentrations from 0.61 to 6.31 μg Kg− 1. Despite the low number and amounts of PPPs determined in sediment, they could serve as a contin- uous source of PPPs to the aquatic environment and biota and pose longterm ecological threats (Akoto et al., 2016).

The accumulation of the detected CECs could be attributed to the low polarity: (logKow ≥ 3 for most of the detected compounds) which facilitate their retention on the river sediment. The variety and relative abundance of the detected CECs could shed light on the major contamination source, such as the industrial production of the frequently detected compounds. However, it should be noted that only 4 sediment samples were investigated in this study, which were insuffi- cient to generate representative outputs for the occurrence profiles of CECs in the DRB. A study covering more sediment samples is required to serve such purposes.

3.4. Biota

The analysis of 22 biota samples (fish muscle) revealed the presence of 9 industrial chemicals, 20 PPPs, and 49 PPCPs and their TPs. This indicates a potential for their persistence and bioaccumulation (P and B criteria) according to the REACH legislation (European Parliament and Council: Registration, 2006). Steroids were not reported for biota sam- ples, as they are naturally occurring compounds in fish.

In total, 15 PPCPs were detected in only one of the 22 biota samples. The most abundant PPCPs detected in biota were vigabatrin, benser- azide and apophedrin, with maximum detected concentrations of 121, 184 and 185 μg Kg− 1 wet weight, respectively. On the other hand, 40 (82%) of the detected PPCPs were found at lower levels (<40 μg kg− 1). The total cumulative concentration among the tested biota samples ranges from 154 (JDS4-43-L-FC in Bulgaria) to 483 μg kg− 1 (JDS4-49-RFC in Romania).

Among the 9 detected industrial chemicals in biota, N-methyl-2pyrrolidone showed FoA of 100% with average concentration of 22 μg kg− 1. The compound was not found in the studied river water samples, source identification could be vital due to the ubiquitous presence of Nmethyl-2-pyrrolidone. The Danube RBSP PFOS was detected with FoA 64% and maximum concentration of 41 μg kg− 1 (JDS4-6.2-Y-FC in Germany). Two PFASs were detected in biota and not in river water: perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnA). Both of them were detected with much lower FoA of 27.3% and at low average concentrations of 1.1 μg kg− 1.

Three of the 20 detected PPPs showed FoA ≥ 50% in the studied biota samples, including barban, methoprene and 3-hydroxy-
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Fig. 3. Venn diagram showing occurrence of identified CECs in the studied DRB environmental matrices.
carbofuran, with average concentration of 25, 5.3 and 3.6 μg kg− 1, respectively. Alachlor-OXA and pyrethrin I were the fourth most frequently detected PPPs in biota (both with FoA 36%), which was detected at average concentration of 11 and 23 μg kg− 1, respectively. The 15 other PPPs were detected in the samples with FoA below 20% (present in only 1-4 of the 22 biota samples).

The presence of CECs in biota samples in the DRB could pose threats to both public health and the ecosystem. Some of the detected PPCPs and PFASs possess a high bioaccumulation potential in aquatic biota and could reach higher level predators (including human) via the food web (Olsvik et al., 2019; Xie et al., 2017). Some of the detected PPPs could inhibit cholinesterase activity and cause inflammatory responses in fish, and they could also bioaccumulate in fish and the food chain (European Commission: Commission Implementing Decision (EU), 2018). Contin- uous monitoring of CECs in biota of the DRB are recommended, in particular the ones prioritized in the ecotoxicological risk assessment of this study (see Section 3.7).

3.5. Influent and effluent wastewater

Influent and effluent wastewater samples (24h-composite reflecting the hydraulic retention time of each WWTP) were compared to obtain removal rate of compounds. In order to draw robust results from the dataset, the analysis on removal rate was restricted to substances that were detected in at least six out of the 22 (11 influent and 11 effluent) wastewater samples (n = 212). The result is included in the "Wastewater analysis" tab of the supplementary material. WWTPs showed efficient (removal rate ≥80%) and medium (removal rate 25-80%) removal for 79 (37%) and 35 (17%) out of the 212 CECs. It should be noted that the low or negative removal rates may not imply poor removal efficiency for some compounds, as they could be TPs produced during the treatment process of other CECs (biodegradation, denitrification, ozonation, etc.). For instance, guanylurea, citalopram N-oxide and cetirizine-N-Oxide, are transformation products of metformin, citalopram and cetirizine, respectively. They could be produced during the treatment
process of the parent compounds which resulted in the low or negative removal rates. This could account for the negative removal rate observed in 89 of the 212 compounds (42%).
Some PPCPs detected in the effluent wastewater samples are on various Watch Lists. 17beta-estradiol is included in the Watch List established by the Commission Implementing Decision (EU 2018/840) (European Commission: Commission Implementing Decision (EU),
2018). It was detected in five effluent wastewater samples at levels from 2.02 to 4.04 ng L− 1. Five other compounds on the updated Watch List of 2022 (EU 2022/1307) (Commission Implementing Decision, 2022) were also detected in the effluent wastewater samples, including Amoxicillin (90–273 ng L− 1), ciprofloxacin (29–617 ng L− 1), sulfamethoxazole (103–1638 ng L− 1), trimethoprim (<LOQ-89 ng L− 1), and fluconazole (7–23 ng L− 1).
Twenty compounds were selected as performance indicators for evaluation of performance of WWTPs in the wastewater abatement process. Fig. 2 demonstrates the removal rate of the 20 selected indicator substances. One of the 20 indicators, diclofenac, has already been assigned as Danube RBSP (Liˇska et al., 2015). Six out of the 20 indicator substances were efficiently removed by WWTPs (removal rates ≥80%). Medium removal rates (25-80%) were observed for eight indicator substances as shown in Fig. 2. Negative removal rates indicate higher levels of compounds detected in effluent wastewater than in influent wastewater (observed in 5 indicators). This phenomenon is sometimes observed for TPs (for example, the industrial chemical methylbenzo- triazole is also a TP of benzotriazole) or compounds which are cleavage products of other substances (Brown and Wong, 2018). Carbamazepine is a TP of its conjugated substances, which could be re-transformed into free form (carbamazepine) during biological treatment, resulting in
negative removal (Kumar et al., 2022). WWTPs were proven to facilitate the protection of the Danube River ecosystems by providing medium/-effective removal to 70% of the indicator substances. Nevertheless, more efficient treatment techniques should be established to achieve better removal of contaminants.
Selection of WWTPs by the ICPDR was based on the size of popula- tion served and the dominant wastewater treatment technology of the country, with the aim to get representative view on the WWTPs of the DRB. The 11 studied WWTPs all involve activated sludge system using sequencing batch reactors, with reaction processes to remove carbon, nitrogen and phosphorous. Such system setup is promising for removal of biological nutrient and organic compounds (Dutta and Sarkar, 2015). Nonetheless, further environmental studies covering a wider variety of WWTP removal systems such as the ones with submerged aerated filter system and rotating disc system could yield more comprehensive comparison of efficiency of different treatment plant systems. Future investigation on removal efficiency of WWTPs at catchment level could shed light on their role in contaminant emission in the studied area. Such study would suggest goals for improvement in removal techniques of WWTPs at the DRB.
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Table 1 Compounds with PNEC exceedance in JDS4 river water, sediment and biota samples.
River water Compound
Pyrethrin I^ Carbamazepine ^(LS) Benzododecinium (Benzyl-dimethyl-
dodecylammonium) ^ 4-tert-Octylphenol (4-t-OP) ^(LS) PFOS ^(LS) Carbendazim ^ Dazomet Metazachlor ^ Dicloxacillin ^ Diclofenac ^(LS) Imidacloprid ^(LS) Candesartan ^ Methoprene ^ Pethoxamide ^ Terbuthylazine ^ Bisphenol A bis(3-chloro-2-hydroxypropyl) ether 2,4-D Terbuthylazin-2-hydroxy Imazamox pp-DDE ^ pp-DDD ^ Nicosulfuron Phosphate-2-Ethylhexyl diphenyl (EHDP) ^ 17beta-Estradiol ^(LS)
PNECfw (ng L− 1)
1.40 50* 62.00
100* 0.65* 150.00 38.00 20.00 5.10 50* 8.3* 3.10 1.40 0.49 60.00 340.00 20.00 7.30 11.00 0.40 0.50 9.00 18.00 0.4*
Number of samples >PNEC
1 4 49
5 46 11 1 3 1 2 7 8 8 35 4 1 2 23 1 4 1 4 6 5
Maximum detected concentration (ng L− 1)
3.00 57.6 11279
124.13 11.5 1523 38.2 29.3 5.49 63.2 39.9 31.2 40.4 16.5 87.1 536 943 121 26.0 2.74 0.82 47.1 53.6 2.10
Sample with highest concentration (country)
JDS34 (HR) JDS15 (SK) JDS24 (HU)
JDS27 (HU) JDS12 (CZ) JDS36 (RS) JDS48 (BG) JDS12 (CZ) JDS13 (SK) JDS15 (SK) JDS46 (BG) JDS34 (HR) JDS37 (RS) JDS12 (CZ) JDS11 (CZ) JDS4 (DE)
JDS36 (RS) JDS46 (BG) JDS46 (BG) JDS46 (BG) JDS13 (SK) JDS49 (RO) JDS51 (UA) JDS13 (SK)
Sediment Compound
PNECsed (µg kg d. w.− 1)
Number of samples >PNEC
Maximum detected concentration (µg kg d.w.− 1)
Sample with highest exceedance (country)
Carbamazepine (LS) Benzododecinium (Benzyl-dimethyl-
dodecylammonium) Octocrylene (LS) Bis-(2-ethylhexyl)-Phthalate (DEHP) (LS) 4-tert-Octylphenol (4-t-OP) (LS) Sulfadiazine Sulfaclozine N-Methyldodecylamine Apophedrin (Phenylethanolamine) N,N-Dimethyltetradecylamine Barban Methiocarb (Mercaptodimethur) (LS) Fenbendazole Cadusafos
1.7 0.1

52.4 0.0077 12.3 7.29 17.00 9.05 205.00 6.11 83.1 0.12 8.4 0.031
1 4
3 4 1 2 1 2 1 1 1 2 2 1
4 19
162 1,342 26 120 32 540 213 17 84 6 26 1
JDS4-6 (DE) JDS4-6 (DE)
JDS4-47 (BG) JDS4-24 (HU) JDS4-51 (UA) JDS4-47 (BG) JDS4-47 (BG) JDS4-24 (HU) JDS4-6 (DE) JDS4-24 (HU) JDS4-47 (BG) JDS4-51 (UA) JDS4-6 (DE) JDS4-24 (HU)
Biota Compound
PNECbio (µg kg w. w.− 1)
Number of samples >PNEC
Maximum detected concentration (µg kg w. w.− 1)
Sample with highest exceedance (country)
Pyrethrin I Vigabatrin Bis-(2-ethylhexyl)-Phthalate (DEHP)
(LS) Sulfamethoxazole (LS) 4-tert-Octylphenol (4-t-OP) (LS) PFOS (LS) Sulpiride Temazepam Niflumic acid Methoprene Apophedrin (Phenylethanolamine) Lovastatin Propoxur Imazamox Barban Cytarabin Imazapyr Trapidil
1.67 54.2 1.33
15.9 19.9 0.0022 5.87 2.9 1.65 0.1 181.00 4.52 0.046 0.064 51.9 16.00 0.061 2.99
8 9 15
1 9 14 8 1 2 13 1 6 1 3 1 8 3 11
34 121 134
29 99 41 52 4 2 8 185 18 1 2 81 75 31 97
JDS4-2 (DE) JDS4-2 (DE) JDS4-6.2 (DE)
JDS4-23 (HU) JDS4-40 (RO) JDS4-6.2 (DE) JDS4-29 (HU) JDS4-23 (HU) JDS4-6 (DE) JDS4-16 (SK) JDS4-49 (MD) JDS4-29 (HU) JDS4-49 (MD) JDS4-6 (DE) JDS4-6.2 (DE) JDS4-2 (DE) JDS4-6.2 (DE) JDS4-30 (SI)
* Environmental quality standard (EQS). ^ CECs in river water also observed in WWTP effluent discharge (LS) Legacy substances (previously proposed Danube RBSPs, WFD priority substances or Watch List candidates).
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3.6. CECs in the DRB: the whole story
Overall, 339 out of the 586 detected compounds were found in more than one of the JDS4 environmental matrices as shown in Fig. 3. Commonly detected PPPs, industrial chemicals and PPCPs are summa- rized in the “Commonly detected CECs” tab of the supplementary ma- terial, along with the matrices in which they were detected. Benzododecinium, 4-t-OP (WFD priority substance (ECHA Substance Infocard - 4-(1,1,3,3-tetramethylbutyl)phenol. 2021), sulpiride, and galaxolidone were detected in all of the studied environmental matrices. Among them 82 compounds were commonly detected in river water, wastewater and groundwater, while additional 121 and 26 compounds were commonly detected in river water/wastewater and groundwa- ter/wastewater, respectively. This finding indicates a possible link in contamination profiles between these aquatic matrices. Contaminants that are not removed or degraded in WWTPs could be introduced to river water and/or groundwater of the DRB (Kosma et al., 2014; Oluwole et al., 2020). These compounds
show high mobility and could pose threats to the environment (direct effects on aquatic organisms) and human (consumption of drinking water produced from groundwater). For instance, exposure to PFASs via polluted drinking water has been associated with increased incidence of tumours, hormone disruption, and adverse reproductive outcomes in humans and other animals (Gonsioroski et al., 2020).
In total, 33 CECs were detected in both river water and biota sam- ples, which indicates the high potential for bioaccumulation of these compounds. They pose potential health risk to various trophic levels and especially to top predators in the food web (including humans) through fish consumption (Ahrens and Bundschuh, 2014). Significant increase in human cancer risk could be potentially associated with the consumption of pesticide polluted fish (Gerber et al., 2016). Among the 33 contami- nants, seven were not detected in wastewater samples (vigabatrin, rivastigmine, tramadol-nor (Tramadol-N-desmethyl), 4-piperidinecar- boxamide, benserazide, metolachlor met (Metolachlor OA, CGA 351916/CGA 51202), imazamox), which suggests sources other than WWTPs discharge or analytical reasons such as concentration below LOD. It was found that sewage discharge, hospitals and pharmaceutical manufacturing facilities are common sources of pharmaceutical pollu- tion in river water (Wilkinson, 2022). Agriculture, aquaculture, and
forestry could contribute to PPPs in aquatic biota and ecosystems (Sid- diqui, 2018). Sewage discharges and industrial wastes are the major contributors of industrial chemicals in river water and aquatic biota (Bashir et al., 2020). The other 26 compounds were also detected in wastewater samples, indicating that WWTP discharge could be a point source of such compounds on top of the aforementioned sources. Further studies are required to accurately identify sources of these compounds in the DRB.
The present study utilizing target screening provides insights on the 586 detected contaminants at the DRB (full list available in the “Detected compounds” tab of the supplementary material). Suspect screening has been proven to be a powerful analytical to reveal CECs in environmental samples, which is a great complement to target screening (Hug et al., 2014). Complementary suspect screening of the JDS4 sam- ples was performed which covered >65,000 CECs and their TPs (NOR- MAN: JDS4 Suspect Screening, 2022). The NORMAN Network has been working on the harmonization of the suspect screening approach. The suspect list exchange (SLE) platform (Taha, 2022; NORMAN Suspect List Exchange – NORMAN SLE 2015) established by the NORMAN Network includes various suspect lists of CECs, which enables suspect screening of thousands of CECs in environmental samples. For instance, suspect screening revealed the presence of 72 additional PFASs in JDS4 samples in another study (Ng et al., 2022). Future investigation involving both
target and suspect screening would yield more comprehensive results on the occurrence, source and fate of CECs present in the environment.
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3.7. Risk assessment

The measured concentrations of all the detected compounds were compared to their lowest PNEC values retrieved from the NORMAN Ecotoxicology database (Dulio, 2020), which contains PNECs for freshwater, marine waters, sediments and biota. Table 1 summarizes the list of compounds that exceeded their PNECs in the JDS4 river waters, sediments and biota samples. All substances listed in Table 1 require further attention of the regulators and the researchers. One should note that 18 out of the 24 CECs detected with PNEC exceedance in river waters originated (at least partially) from WWTP effluent discharge (indicated with ^ in Table 1). Among the prioritized 45 CECs, 12 are legacy substances (indicated with (LS) in Table 1) which are previously proposed Danube RBSPs, WFD priority substances or Watch List candi- dates. The other 33 emerging contaminants determined in the risk assessment are candidates for Danube RBSPs.
Some prioritized PPPs (e.g. barban and imazapyr) were detected in biota samples at highest concentration in German sites. These com- pounds are not in the list of Authorised Plant Protection Products of the German Federal Office of Consumer Protection and Food Safety (Infor- mation on Authorised Plant Protection Products, 2023) and were not in use e.g. in Germany for the last decades. This is indicative of pollution sources other than agricultural activities.

4. Conclusions

A novel approach was presented demonstrating the usefulness of wide-scope target screening of 2362 PPPs, industrial chemicals, PPCPs and their TPs in influent and effluent wastewater, river water, ground- water, sediments and biota samples collected in the JDS4. Such appli- cation of chemical screening provided insight on the potential source and fate of a wide spectrum of CECs in the DRB, facilitated the perfor- mance evaluation of studied WWTPs, and revealed the potential can- didates for Danube RBSPs. The application of HRMS screening methodology revealed the presence of 586 of these chemicals in the JDS4 samples, including 158 PPPs, 71 industrial chemicals, 348 PPCPs, and nine other chemicals. The removal of contaminants by WWTPs was investigated, their fate in the catchment was reported. WWTPs were proven to effectively remove (removal rate ≥80%) 6 of the 20 indicator chemicals selected to evaluate performance of WWTP. Medium removal rates (25–80%) were observed for eight indicator substances. WWTPs managed
to significantly reduce concentration levels of the vast ma- jority of studied contaminants. Nevertheless, some contaminants passed WWTPs unaltered in the effluent discharges. More efficient treatment techniques are required to improve removal of contaminants at WWTPs. Effluent wastewater, sewage discharge, and other anthropogenic activ- ities (e.g. industrial production and agricultural activities) are among the major sources of CECs in the DRB. Attention was drawn to 19 PPPs, 8 industrial chemicals and 18 PPCPs that exceeded their respective eco- toxicological thresholds in various matrices. 33 of them are emerging contaminants and thus qualify as Danube RBSPs. As the number of samples provides only a snapshot of the distribution of CECs in various matrices, single outstanding results have to be verified by additional investigations. Continuous monitoring programme in the DRB would help to keep these CECs at acceptable levels in the studied area by triggering mitigation measures.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Data was included as supplementary material.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2022.119539.

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