THE CLER REVIEW

Research **Technology** **Public Policy**

Volume 18, Number 2

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THE
CLER
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VIEW

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Volume 18, Number 2

EDITOR'S PREFACE:
THE WRONGHEADED FOCUS OF THE MAF ON REACH CHEMICALS

This issue of *The CLER Review* follows up *The CLER Review Vol. 18 No. 1* (https://cler.com/the-cler-review/) in examining the available science regarding the European Commission (EC) proposal to apply a mixture assessment factor, also called a mixture allocation factor (MAF) to every chemical requiring a quantitative risk evaluation in the REACH Chemicals Regulation database. That database now consists of over 26,000 chemicals. The data analysis and commentary in this issue notes pesticides and pharmaceuticals are far more likely to be identified as drivers of environmental risk, challenging the EC policy decision to apply the MAF first to the REACH database.

The Additional Data and Commentary provided in this *issue* focuses on the data in a United Kingdom (UK) Government report (2022) and a recent review of European monitoring data (Rodea-Palomares et al. 2023). The UK Government report reviewed 15 studies of mixtures of chemicals in environment monitoring studies. The Rodea-Palomares et al. review examined all of the available monitoring data from the largest freshwater databases in the EU, the Waterbase – Water Quality ICM database (https://www.eea.europa.eu/data-and-maps/data/waterbase-water-quality-icm-1). Data were found on over 300 individual chemicals detected in over 14,000 environmental samples. Both the UK Government report (2022) and the Rodea-Palomares et al. (2023) review focused on identifying risk drivers, chemicals detected in the aquatic environment at levels that exceeded Water Quality Criteria, predicted no effect concentrations (PNECs) or other indicators of potential risk to aquatic organisms.

The UK Government report also reviewed a modeling study (Posthuma et al. 2019) that used predicted environmental concentrations to examine potential mixture risk from over 1700 chemicals including industrial chemicals and pesticides. The conclusion of the study was that 15 chemicals - 10 industrial chemicals and 5 pesticides - accounted for over 99% of the predicted risk in mixtures.

The overall conclusion from the data in the UK Government report and the Rodea-Palomares et al. review is that the most frequently detected risk drivers are pesticides and pharmaceuticals along with a few industrial chemicals.[1]

The finding that the most frequently found drivers of environmental risk are pesticides and pharmaceuticals is perhaps not surprising. Pesticides and pharmaceuticals

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[1] It should be noted that conclusions on frequency of detection are limited by analytical methods in the case of monitoring studies and by the available exposure and hazard data in the case of the modeling study (Posthuma et al. 2019).

are designed to be bioactive, and thus may have appreciable aquatic toxicity as a consequence of their intended (and highly beneficial) effects. Pesticides are used primarily on agricultural fields and thus have the potential to be widely dispersed in the environment. Pharmaceuticals may also be widely used, with the potential to end up in human waste and thus in wastewater treatment plants (WWTPs). Pesticides are designed to have adequate stability in the environment to reach their intended targets (pests) and deliver their intended effect/benefit. Consequently, pesticides may be resistant to biodegradation by microorganisms in the environment.[2] Similarly, pharmaceuticals are designed to have adequate stability in the human body to reach their intended tissues/organs and deliver their intended effect/benefit. Consequently, pharmaceuticals may be resistant to biological treatment (aerobic biodegradation), the main treatment method in WWTPs.

These considerations also explain why only a relatively few industrial chemicals are identified as drivers of environmental risk as most industrial chemicals are not designed for bioactivity, or to be stable in biological systems. Indeed, the cleaning agents (surfactants) used in laundry detergents and cleaning products, which do have bio-activity as a consequence of their surfactant activity, are designed to have rapid (ready) biodegradability and high removal rates in WWTPs, exceeding 99% for the major surfactants (Cowan-Ellsberry et al. 2014). Any residual levels found in effluents and biosolids (sludge) will completely biodegrade in receiving waters and sludge-amended soil. This conclusion of rapid and complete biodegradation has also been demonstrated for environmental mixtures of surfactants. See the linear alkylbenzene sulfonate (LAS) case study in *Vol. 18 No. 1* (https://cler.com/the-cler-review/) for a complete review and assessment of the environmental mixture data on the largest volume surfactant used in laundry and cleaning products.[3]

Among the few industrial chemicals found to be risk drivers, many are already highly regulated, or are candidates for further regulation. It is difficult to see how addition of the MAF to the risk evaluation of these chemicals will increase risk management and further protect the environment.

In short, the data in the Additional Data and Commentary do not support the proposed application of the MAF to every chemical in the REACH database, and instead indicate the MAF value should be applied in a more focused assessment. The data indicate that industrial chemicals in the REACH registration database should not be the only focus to identify those few chemicals which contribute to environmental mixture risk.

— John Heinze, Ph.D.
Editor, *The CLER Review*

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[2] It should be noted that this statement is not accurate for all pesticides. Some of the new generation pesticides are designed to rapidly breakdown in the environment after reaching their intended targets.

[3] A just published study (Briels et al. Sci. Total Environ. 167322, on-line 25 Sept. 2023) assessed the contribution of surfactants to mixture toxicity in French surface waters. The study concluded that "surfactants contributed minimally to the mixture risk in investigated water bodies."

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ADDITIONAL DATA AND COMMENTARY: INVESTIGATION OF THE SCIENTIFIC BASIS FOR THE PROPOSED APPLICATION OF A MIXTURE ASSESSMENT FACTOR (MAF) TO EVERY CHEMICAL IN THE EU REACH CHEMICALS REGISTRATION PROGRAM

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SUMMARY

A previous manuscript (Heinze and Dyer, 2023) examined the scientific basis for the proposed application of a mixture assessment factor, also call a mixture allocation factor (MAF) to every chemical in the EU REACH Chemicals Registration Program. This manuscript considers whether there is clear evidence to support application of a MAF to the REACH chemicals registration database (26,000+ industrial chemicals) before application to any other regulatory program, such as for pesticides or pharmaceuticals. The data in a UK Government report (2022) and a recent environmental monitoring study (Rodea-Palomares et al. 2023) were reviewed to assess this question.

The UK Government report reviewed 16 studies on environmental mixtures in the EU and the UK, including a study of modeled environmental concentrations (Posthuma et al. 2019) and 15 environmental monitoring studies. The modeled concentrations study reported that 15 chemicals, all industrial chemicals and pesticides, accounted for 99% of all mixture risk. The 15 monitoring studies and the Rodea-Palomares et al. study reported that most drivers of mixture risk were pesticides or pharmaceuticals.

The reviewed data indicate: 1) relatively few chemicals have been identified as potential drivers of environmental mixture risks; and 2) many of the industrial chemicals identified as risk drivers are already undergoing increased risk management or are candidates for increased risk management.

These data do not support the proposed application of the MAF to every chemical in the REACH database, and instead indicate the MAF value should be applied in a more focused assessment. The data reviewed in this commentary indicate that industrial chemicals in the REACH registration database should not be the only focus to identify those few chemicals which contribute to environmental mixture risk.

INTRODUCTION

A previous manuscript (Heinze and Dyer, 2023) examined the scientific basis for the proposed application of a mixture assessment factor, also called a mixture allocation factor (MAF) to every chemical in the EU REACH Chemicals Registration Program (European Commission 2020). The manuscript reviewed the available data on linear alkylbenzene sulfonate (LAS), a major surfactant used in laundry and cleaning products, for which there is likely more environmental mixture data than any other down-the-drain disposal chemical in the REACH database. The data from the LAS case study do not support application of the MAF to every chemical in the REACH database. Instead, the analyses support the suggestion from numerous authors, e.g., van de Meent et al. 2020, that a MAF value should be applied in a more focused assessment, consistent with the observation that relatively few chemicals are responsible for environmental impacts.

The Chief Scientist's Group of the United Kingdom (UK) government recently prepared a report to evaluate potential risk from unintentional (environmental) chemical mixtures and possible future application to the UK REACH program (UK Government 2022). The UK Government report concluded that "there is no clear evidence that industrial chemicals contribute to the potential mixture toxicity risk more than chemicals regulated under other regimes. Policy makers will therefore need to consider whether applying a MAF to industrial chemicals alone can be justified." This conclusion poses a scientific challenge to the European Commission (EC) proposal to first apply a MAF to the REACH Registration database (EC 2021).

DATA REVIEW

This manuscript considers whether industrial chemicals such as those in the REACH database should be the initial focus of application of the MAF, or would it be better environmental management to also focus on chemical groups such as pharmaceuticals and pesticides, which are regulated under separate regulatory programs and frequently identified as drivers of chemical risk.

The data in this assessment is taken from two recent publications:

1) The 16 environmental mixture studies reviewed in the UK Government report (2022), and

2) A large-scale study (Rodea-Palomares et al. 2023) on risk from unintentional environmental mixtures in EU surface waters (334 substances, 143,000 samples).

The UK Government report (2022) reviewed 16 studies on environmental mixtures in the EU and the UK. Of these, Posthuma et al. 2019 was a modeling study using predicted exposure concentrations (PECs), while the other 15 studies were monitoring studies using measured environmental concentrations (MECs). In the study using modeled data, PECs were calculated for 5188 chemicals (4159 REACH-registered industrial chemicals, 621 pharmaceuticals and 408 pesticides) using a computational material flow analysis consisting of two steps: (1) simulation of chemical inputs to the environment and (2) simulation of fate and transport of the chemicals in the environment (van Gils et al. 2020). Comparison of PECs with MECs from monitoring studies for 226 substances showed 65% of the PECs were within one order of magnitude of the respective MECs and 90% were within two orders of magnitude. The authors (Gils et al. 2020) concluded "simulated concentrations were accurate on average."

Posthuma et al. (2019) examined the available aquatic toxicity data on the chemicals for which PEC data were available. Adequate data was identified for 1760 of the chemicals. Predicted effects were determined in a three-step process. In the first step, species sensitivity distributions (SSDs) were generated for individual chemicals based on publicly available aquatic ecotoxicity data. These distributions were then used to predict the potentially affected fraction (PAF), the proportion of species expected to be affected at a particular chemical concentration. In the second step, the toxicity of the mixture is calculated as the sum of the PAFs of the individual chemicals present in the mixture, the multi-species PAF (msPAF). A msPAF value of >0.05 is considered unacceptable risk as greater than 5% of species present are expected to be affected. In the third step, relative rankings of chemicals in mixtures with msPAF >0.05 were derived by: 1) normalizing the mean PAF score for each chemical (multiplying the mean score by the ratio of the individual chemical PAF score over the msPAF score for each mixture); 2) calculating a relative ranking by dividing each normalized score by the lowest non-zero PAF score of the mixture and 3) totaling the relative rankings.

Chemicals with the highest total rankings are identified in **Table I**. These 15 chemicals, representing 1% of the total number of ranked chemicals, accounted for over 99% of the risk in mixtures with msPAF >0.05. All of the compounds are characterized by high production mass, ubiquitous use and high hazard classifications.

As noted in Table I, 10 are industrial chemicals and 5 are pesticides. Also as noted, 5 of the 15 have already been identified as REACH substances of very high concern (SVHC) and candidates for authorization (ECHA, 2023) or as priority chemicals for risk management (Water Framework Directive (WFD) and/or NORMAN methods) (Posthuma et al. 2019). These compounds are already a priority for increased risk management, a subsequent process to risk characterization. Consequently, it is not obvious how addition of a MAF to the risk characterization would lead to further increases in risk management and increased environmental protection.

Table I. Top 15 Chemical Drivers of Mixture Risk (Posthuma et al. 2019, Table 4)

Rank	Risk Driver	Chemical Group IC = industrial chemical P = pesticide	Regulatory Status SVHC = REACH Substance of Very High Concern; candidate for authorization (ECHA 2023) WFD (Water Framework Directive) Priority Compound NORMAN (NORMAN methods) Priority Compound
1	Bisphenol A	IC	SVHC, WFD, NORMAN
2	N-1,3-Dimethylbutyl-N'-phenyl-p-phenylenediamine	IC	
3	Chlorpyrifos	P	WFD
4	Anthracene	IC	SVHC, WFD
5	Octamethylcyclotetrasiloxane	IC	SVHC, NORMAN
6	N-(4-Aminophenyl)aniline	IC	
7	Cumene hydroperoxide	IC	
8	Diphenylamine	IC	NORMAN
9	1-Dodecanol	IC	
10	Pyraclostrobin	P	
11	Cyhexatin	IC	
12	p-Phenylenediamine	IC	
13	Dimoxystrobin	P	
14	Terbufos	P	
15	Phrorate	P	

Table II lists the 15 environmental monitoring studies that identified organic chemical drivers of risk. In these studies, the environmental concentrations are measured, and the effects concentrations are determined from WFD Environmental Quality Standards (EQS), predicted no effect concentrations (PNEC) or published

Table II. Environmental Monitoring Studies That Identified Chemical Risk Drivers. Source: UK Government (2022), pp. 23-36.

Study	Scope	Method for Determination of Aquatic Toxicity Effect Levels	Drivers	Chemical Group IC = industrial chemical P = pesticide Ph = pharmaceutical
Price et al. 2012	Surface water and effluents 559 samples 21-123 substances/site	EQS or PNEC (following ECB 2003) for acute/intermittent, or chronic data	Clarithromycin Diclofenac PBDEs[1] Terbuthylazine Terbuthylazine desethyl Tramadol	Ph Ph IC P P Ph
Malaj et al. 2014	River basins 4001 sites Up to 223 organic chemicals	Acute data with lab/field derived AF (10 for acute thresholds; 1000, 100 or 50 for chronic invertebrates, fish or algae thresholds)	Pesticides (not further identified)	P
Backhaus and Karlsson 2014	Effluents 7 WWTPs 26 pharmaceuticals	PNEC based on lowest acute value with AF = 1000	Individual pharmaceuticals not further identified	Ph
Ccanccapa et al. 2016	Ebro River, Spain 24 sampling points Up to 50 pesticides	Acute + chronic data (PPD)	Individual pesticides not further identified	P
Rico et al. 2016	Danube River 55 sites 235 organics and 8 metals	Acute data for daphnids (E-Tox database, De Zwart 2002) or predicted data	None	
Munz et al. 2017	Switzerland, effluents + upstream and downstream 36 targeted analytes + 124 substances detected by non-targeted (screening) analyses	msPAF based on SSDs constructed with EC50 data	Not stated	
Gustavsson et al. 2017a	Swedish marine waters 5 sites 172 organic substances	WFD EQS, regulatory PNEC or PNEC derived from ecotoxicity data, with AF=10 for marine organisms	Irgarol[3] Tributyltin[4] Triclosan[2]	IC IC IC
Gustavsson et al. 2017b	Swedish streams 1308 samples 141 pesticides	Swedish Water Quality Objectives or acute data	Not stated	
Papadakis et al. 2018	Two river basins, Greece 631 samples 103 pesticides	PNEC based on chronic data (PPD) using AF=100, 50 or 10 (for 1, 2, or 3 studies)	Individual pesticides (not further identified)	P
Freeling et al. 2019	33 WWTP effluents, Germany 1564 surfactants	PNEC based on chronic data (AF=10) or predicted acute data (AF=1000)	None*	
Riva et al. 2019	Three rivers, Italy 39 pharmaceuticals, drugs, industrial chemicals and personal care products	PNECs from acute data (literature or predicted) with AF=1000, or chronic data with AFs per ECB 2003	10 individual chemicals including: Bisphenol A[5] 4-Nonylphenol[5] 4-tert-Octylphenol[5]	IC IC IC
Posthuma et al. 2020	50% percentile concentrations predicted for each water body in Europe 24 WFD Priority Substances	1. WFD EQS 2. HC5 from acute SSDs 3. msPAF based on acute SSDs	Chemicals exceeding EQS not further identified.	
Markert et al. 2020	Erft River, Germany 39 sites 153 pesticides, pharmaceuticals and other substances	Acute and chronic data (online databases)	Across all samples, 90% had single substances that exceeded environmental thresholds; top 10 substances include two on REACH database: Bisphenol A[5] Triclosan[2]	IC IC
Gosset et al. 2021	Effluents, France 10 WWTPs 37 pharmaceuticals and 4 pesticides	PNECs (regulatory or published), or calculated from published or predicted data using AFs (ECB 2003)	7 substances (not further identified) contributed nearly 98% of the potential risk	
Spurgeon et al. 2021	UK monitoring data 23000 surface water samples 1144 substances	HC50 from chronic SSDs (Posthuma et al. 2019)	Potential mixture risk driven by small number of substances (2-5); specific substances not identified	

AF = assessment factor; EC50 = 50th percentile effect concentration from acute ecotoxicity study; EQS = Environmental Quality Standard; HC5 = 5th percentile hazard concentration from SSD; HC50 = 50th percentile hazard concentration from SSD; msPAF = multi-species Potentially Affected Fraction; PNEC = predicted no effect level; PPD = Pesticide Property Database (University of Hertfordshire); SSD = species sensitivity distribution; WFD = Water Framework Directive; WWTP=wastewater treatment plant.

* Mixture risk quotients (RQs) below 1 except for one WWTP with RQ = 1.065; LAS PNEC value used 10x lower than REACH assessment; using the LAS REACH PNEC, all RQs <1.

1. PBDEs (polybrominated diphenyl ethers) - ROHS (Restriction of Hazardous Substances in Electrical & Electronic Equipment) Directive: Restricted substance
2. No longer manufactured / imported in the European Economic Area (ECHA 2023).
3. Biocide Products Regulation: No longer approved for use.
4. REACH Annex XVII: no longer allowed on market or used as biocide in paint (ECHA 2023).
5. Classified as a substance of very high concern and a candidate for authorization (ECHA 2023).

acute or chronic aquatic toxicity data using assessment factors (AFs) such as those from REACH (ECB 2003) to convert to PNEC values. Risk drivers that are industrial chemicals are noted (IC). As can be seen, most of the drivers are pesticides (P) or pharmaceuticals (Ph). As noted in the footnotes, the industrial chemicals listed in Table II are restricted substances, no longer manufactured/imported in the European Economic Area, no longer approved for use, or classified as a substance of very high concern (SVHC) and a candidate for authorization. For these industrial chemicals, risk management actions are already in place or have already been triggered. It is unclear how addition of a MAF to the risk characterization for these chemicals would produce additional environmental protection.

Table III lists the chemical risk drivers from the Rodea-Palomares et al. (2023) study. The study examined chemical monitoring data from one of the largest freshwater databases in the EU, the Waterbase – Water Quality ICM database (https://www.eea.europa.eu/data-and-maps/data/waterbase-water-quality-icm-1). The study considered MECs of 334 chemicals detected among the 143,000 samples with quantifiable levels of at least one chemical. MEC values were either the mean or the maximum concentration

Table III. Top 15 Chemical Risk Drivers from Rodea-Palomares et al. 2023. Chemical drivers with at least 5% frequency of occurrence as first, second or third drivers across all monitoring sites, using measured environmental concentration (MEC) values based on median or maximum concentrations at each site for the year.

Chemical Risk Drivers (listed in decreasing order of frequency*)	Usage L = legacy chemicals[#] C = current use (those not legacy chemicals.)	Chemical Group IC = industrial chemical P = pesticide Ph = pharmaceutical PAH = polycyclic aromatic hydrocarbon
Isoproturon	L	P
Ibuprofen	C	Ph
Chlorpyrifos	L	P
Diclofenac	C	Ph
Diuron	L	P
Benzo(b)fluoranthene	L	PAH
Caffeine	C	Ph
Benzo(a)pyrene	L	PAH
Tributyl tin	L	IC
Metolachlor	C	P
Terbuthylazine	C	P
Erythromycin	C	Ph
Endrin	L	P
Bis(2-ethylhexyl) phthalate	L	IC
Diazinon	L	P

* Average of observed frequency based on median and maximum concentrations.

[#] Defined by Rodea-Palomares et al. (2023) as all chemicals listed as Priority Pollutants under the Water Framework Directive (European Community, 2000; European Parliament and Council, 2008), or the Stockholm Convention (UNEP 2019), pesticides not currently approved in the EU (European Pesticides Database: https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en), or those chemicals restricted or a candidate for restriction under REACH Annex XVII (Substances of Very High Concern) (ECHA 2023).

for each monitoring site and each year for which monitoring data were available. Hazard Quotients (HQ) for each chemical were calculated as the MEC (mean or max value) divided by the toxicity benchmarks (BMs) from Posthuma et al 2019. BMs are defined as the 5th percentile of Species Sensitivity Distributions based on chronic (NOEC or EC10) endpoints. Cumulative risk mixture toxicity was examined by calculating the Hazard Index (HI) for each unique monitoring site, where the HI is the sum of the HQs for each chemical present. Risk drivers were identified as environmental mixtures for which HI >1, indicating potential risk. For the 334 chemicals for which environmental monitoring data were available, low complexity environmental mixtures predominated with one to three risk drivers per mixture.

Among the 307 organic chemicals, 15 risk drivers were identified that demonstrated at least 5% frequency of occurrence as first, second or third drivers across all monitoring sites. These top 15 risk drivers were predominately responsible for the cumulative (mixture) risk – when these drivers were excluded from the analysis, 95% of the monitoring sites did not show a concern for cumulative risk, e.g. HI <1. As noted in Table III, these top 15 risk drivers included both current use (C) and legacy (L) chemicals. Legacy chemicals were defined by Rodea-Palomares et al. (2023) as all chemicals listed as Priority Pollutants under the WFD (European Community, 2000; European Parliament and Council, 2008), or the Stockholm Convention (UNEP 2019), pesticides not currently approved in the EU (European Pesticides Database: https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en), or those chemicals restricted or a candidate for restriction under REACH Annex XVII (SVHCs) (ECHA 2023). "Current use" chemicals are those not labeled as "legacy chemicals." Metals and polycyclic aromatic hydrocarbons (PAHs) were also excluded from current use chemicals. As noted in Table III, 9 of the top 15 drivers are legacy chemicals and 6 are current use. The chemicals were also grouped by the authors as industrial chemical (IC), PAH, pesticide (P), or pharmaceutical (Ph). Among the top 15 risk drivers, there are 7 pesticides, 4 pharmaceuticals, 2 PAHs and 2 industrial chemicals. Both industrial chemicals (tributyl tin and bis(2-ethylhexyl) phthalate) are legacy chemicals.

A more in-depth examination of the role of current use industrial chemicals can be conducted by examining Figure 5 of the Rodea-Palomares et al. (2023) study, which lists the top 40 risk drivers. **Table IV** provides a listing of all the current use chemicals among the top 40 risk drivers. All current use chemicals, whether ranked based on medium or maximum concentrations are pharmaceuticals or pesticides.

DISCUSSION

The data and commentary in this manuscript is provided in the context of a case study on LAS, a major surfactant used in laundry and cleaning products (Heinze and Dyer, 2023). LAS was considered because there is likely more environmental mixture data on it than any other down-the-drain disposal chemical in the REACH database. Review of this data did not support application of the MAF to LAS, and by extension to every chemical in the REACH database.

Table IV. Top 40 Chemical Risk Drivers per Rodea-Palomares et al. 2023. Chemicals listed in decreasing order of frequency of occurrence as first, second or third drivers across all monitoring sites, using measured environmental concentrations (MEC) values based on either median (A) or maximum (B) concentrations at each site for the year. Only current use chemicals listed. See Table III for definition of "current use."

A. Median Concentrations. Data from Fig. 5A, Rodea-Palomares et al. 2023.

Currently Used Chemicals Among Top 40 Chemical Risk Drivers	Rank Order of Frequency of Occurrence	Chemical Group*
Ibuprofen	1	Ph
Diclofenac	3	Ph
Caffeine	6	Ph
Erythromycin	8	Ph
Metolachlor	10	P
Terbuthylazine	12	P
Azithromycin	16	Ph
Malathion	26	P
Carbamazepine	36	Ph
Ethinyl estradiol	39	Ph

B. Maximum Concentrations. Data from Fig. 5B, Rodea-Palomares et al. 2023.

Currently Used Chemicals Among Top 40 Chemical Risk Drivers	Rank Order of Frequency of Occurrence	Chemical Group*
Ibuprofen	3	Ph
Diclofenac	5	Ph
Caffeine	8	Ph
Metolachlor	9	P
Terbuthylazine	11	P
Erythromycin	18	Ph
Metribuzin	25	P
Malathion	31	P
MCPA	34	P

*All chemicals classified as either industrial chemical (IC), polycyclic aromatic hydrocarbon (PAH), pesticide (P), or pharmaceutical (Ph).

This manuscript examines the available data from environmental modeling and mixture studies which attempted to identify chemicals in the environment capable of producing risk to aquatic organisms via their presence in unintentional mixtures. The modeling study of Posthuma et al (2019) predicts that 99% of environmental mixture risk is caused by 15 industrial chemicals and pesticides (Table I). The 15 environmental monitoring studies reviewed in the UK Government report (Table II) and the data of Rodea-Palomares et al. (Tables III and IV) indicate that pesticides and pharmaceuticals, along with a few industrial chemicals are the major drivers of mixture risk.

The modeling and the monitoring studies agree that a small number of chemicals are drivers of environmental mixture risk. This conclusion has been noted before and termed the Pareto principle (e.g., van de Meent et al. 2020) whereby a small number of inputs, in this case environmental chemicals, are responsible for the large majority of effects, in this case drivers of mixture risk. In the monitoring studies, typically 1-3 chemicals are risk drivers for each mixture examined. In the modeling study, 15 of the 1760 chemicals examined are predicted to be responsible for 99% of the mixture risk.

The risk drivers identified in the monitoring studies differ (compare Tables II, III and IV) as expected based on differences in the individual chemicals tested. Only one chemical predicted as a risk driver in the modeling study (bisphenol A) was identified in monitoring studies. Nonetheless, there is consistency among the monitoring studies and the modeling study that many of the industrial chemicals identified as risk drivers are already undergoing increased risk management or are candidates for increased risk management. It is not obvious how addition of a MAF to the risk characterization for these industrial chemicals would trigger additional environmental protection.

CONCLUSIONS

The data available from environmental monitoring and modeling studies support the conclusion of the UK Government report (2022) that "there is no clear evidence that industrial chemicals contribute to the potential mixture toxicity risk more than chemicals regulated under other regimes."

Furthermore, the reviewed data indicates: 1) relatively few chemicals have been identified as potential drivers of environmental mixture risks; and 2) many of the industrial chemicals identified as risk drivers are already undergoing increased risk management or are candidates for increased risk management. It is unclear how addition of a MAF to the risk characterization of these chemicals would increase environmental protection.

These data do not support the proposed application of the MAF to every chemical in the REACH database, and instead indicate the MAF value should be applied in a more focused assessment. The reviewed data indicate that industrial chemicals in the REACH registration database should not be the only focus to identify those few chemicals which contribute to environmental mixture risk.

ACKNOWLEDGMENT

My thanks to Scott D. Dyer, LeTourneau University, Longview, Texas, USA, for review and comments on the draft manuscript.

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About CLER

Mission

The Council for LAB/LAS Environmental Research (CLER) is a non-profit organization founded in 1988. CLER's mission is to conduct research and communicate information regarding the environmental and human safety of linear alkylbenzene sulfonate (LAS), the world's number one cleaning agent (surfactant), and linear alkylbenzene (LAB), the material used to produce LAS.

Contact Information

CLER has offices in Washington DC, USA and, since January 2018, in Brussels, Belgium. For further information on CLER, please see our website at: www.cler.com

About LAS

Key Ingredient

LAS is a key cleaning ingredient in laundry and cleaning products worldwide. LAS is often used as the main cleaning agent (surfactant) in these products.

"Green" Cleaning

LAS can be considered the first "Green" surfactant as it was introduced in the mid-1960s as a more biodegradable replacement for branched alkylbenzene sulfonate, a poorly biodegradable cleaning agent that's large scale use led to foaming and other problems in sewage treatment plants.

Extensively Studied Safety

The environmental and human safety attributes of LAS have been extensively studied for decades. LAS is probably the best studied cleaning ingredient used in down-the-drain consumer products. Research on LAS is continuing because of its widespread use. LAS is often included as a reference compound in methods development studies because its environmental and health safety properties are so well known.

These studies continue to demonstrate the environmental and human safety and acceptability of LAS use.

About *The CLER Review*

In 1995, CLER began publication of *The CLER Review* to bring together in one publication all of the key studies and scientific information on the environmental and human safety of LAB/LAS. To accomplish this goal, the journal includes previously published studies as well as original commentaries and review articles. All published studies are from the peer-reviewed scientific literature and published with the permission of the journal publishers. Original commentaries are reviewed by journal editor Dr. John Heinze, as well as invited reviewers selected from among the CLER membership.

The CLER Review is freely available upon request. For copies, please see the CLER Review webpage, https://cler.com/the-cler-review/.

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