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# Stable isotope composition of pesticides in commercial formulations: The ISOTOPEST database

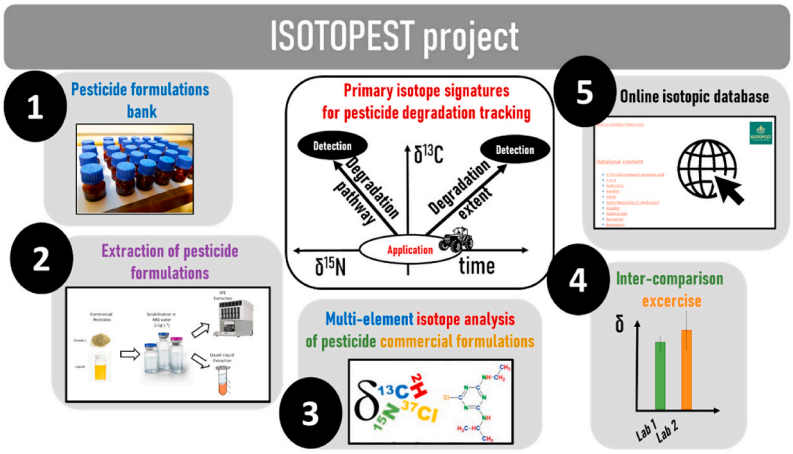
Jérémy Masbou [a], Patrick Höhener [b], Sylvain Payraudeau [a], Fabrice Martin-Laurent [c], Gwenaël Imfeld [a,*]

[a] CNRS, ENGEES, Institut Terre Et Environnement de Strasbourg (ITES, UMR 7063), Université de Strasbourg, Strasbourg, France
[b] CNRS, UMR 7376, Laboratory of Environmental Chemistry, Aix Marseille University, Marseille, France
[c] Institut Agro Dijon, INRAE, Université Bourgogne Franche-Comté, Agroécologie, Dijon, France

## HIGHLIGHTS

- Collection of 120 active substances from commercial pesticide formulations for CSIA.
- Validation of two extraction methods for CSIA from pesticide formulations.
- Carbon and nitrogen CSIA of active substances from 84 formulations.
- Exploration of variability in isotope compositions of active substances across formulations.
- Stable isotope composition of commercial pesticides for source identification and process elucidation.

## GRAPHICAL ABSTRACT

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## ABSTRACT

By assessing the changes in stable isotope compositions within individual pesticide molecules, Compound Specific Isotope Analysis (CSIA) holds the potential to identify and differentiate sources and quantify pesticide degradation in the environment. However, the environmental application of pesticide CSIA is limited by the general lack of knowledge regarding the initial isotopic composition of active substances in commercially available formulations used by farmers. To address this limitation, we established a database aimed at cataloguing and disseminating isotopic signatures in commercial formulations to expand the use of pesticide CSIA. Our study involved the collection of 25 analytical standards and 120 commercial pesticide formulations from 23 manufacturers. Subsequently, 59 commercial formulations and 25 standards were extracted, and each of their active substance was analyzed for both $\delta^{13}C$ (n = 84) and $\delta^{15}N$ CSIA (n = 43). The extraction of pesticides did not cause significant isotope fractionation ($\Delta^{13}C$ and $\Delta^{15}N$ < 1‰). Incorporating existing literature data, stable carbon and nitrogen isotope signatures varied in a relatively narrow range among pesticide formulations for

* Corresponding author.
*E-mail address:* imfeld@unistra.fr (G. Imfeld).

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different pesticides ($\Delta^{13}C$ and $\Delta^{15}N < 10‰$) and within different formulations for a single substance ($\Delta^{13}C$ and $\Delta^{15}N < 2‰$). Overall, this suggests that pesticide CSIA is more suited for identifying pesticide transformation processes rather than differentiating pesticide sources. Moreover, an inter-laboratory comparison showed similar $\delta^{13}C$ ($\Delta^{13}C \leq 1.2$ ‰) for the targeted substances albeit varying GC-IRMS instruments. Insignificant carbon isotopic fractionation ($\Delta^{13}C < 0.5‰$) was observed after 4 years of storing the same pesticide formulations, confirming their viability for long-term storage at 4 °C and future inter-laboratory comparison exercises. Altogether, the ISOTOPEST database, in open access for public use and additional contributions, marks a significant advancement in establishing an environmentally relevant pesticide CSIA approach.

## 1. Introduction

Assessing the transformation extent and pathways of pesticide residues within the environment stands as a crucial facet of pesticide management. This evaluation serves to identify potential risks and to offer insights essential for water management decisions. By leveraging estimates of active substance concentrations in the commercial formulation alongside known concentrations of pesticide transformation products (TPs), mass balance calculations are commonly employed to assess pesticide dissipation processes within the environment (Lefrancq et al., 2017; Imfeld et al., 2021). However, the assessment of pesticide dissipation in agro-ecosystems faces significant limitations due to intricate hydrological dynamics and complex transport processes. Depending solely on concentration trends presents challenges, as both non-degradative dissipation processes, such as dilution and sorption, and degradative processes contribute to the apparent reduction in pesticide concentrations in the field. This may severely bias field estimations of pesticide persistence and transformation.

In this context, compound-specific isotope analysis (CSIA) of pesticides has emerged as a complementary line of evidence to evaluate pesticide degradation and persistence in water and soil of agricultural catchments (Elsner and Imfeld, 2016). CSIA allows to evaluate changes of the natural stable isotope composition of the residual, non-degraded fraction of a pesticide to evaluate degradation without considering concentration data of parent compound or transformation products (Kuntze et al., 2020; Chen et al., 2022). The environmental application of pesticides CSIA has recently advanced due to validated extraction methods from diverse matrices such as soils, sediments, and waters (Torrentó et al., 2019; Gilevska et al., 2022; Suchana et al., 2024), and the introduction of sensitive gas chromatography isotope ratio mass spectrometry (GC-IRMS). The relevance of pesticide CSIA to trace pesticide transformation processes in the environment lies in the observation that changes in isotope ratios at natural abundance during pesticide transformation are specific to the chemical reaction. In addition, combining the utilization of several stable isotopes in a multi-element compound-specific isotope analysis (ME-CSIA) approach (Meyer et al., 2009; Ivdra et al., 2017; Drouin et al., 2021; Torrentó et al., 2021; Junginger et al., 2022) can prove instrumental in differentiating between transformation pathways in environmental settings (Höhener et al., 2022).

Efficient application of pesticide CSIA in field studies necessitates the determination of the primary isotopic signature (Hunkeler et al., 2008). In this case, the primary isotopic signature represents the isotopic composition of the target pesticide in its commercial formulation used by farmers before undergoing isotope fractionation during pesticide transformation in the field. The primary isotope signature is then confronted to the measured signature in the field in order to prove and quantify pesticide degradation. Since the primary isotopic signature in laboratory experiments generally consists of pure analytical standards, they dominate the currently known stable isotope compositions of pesticides (Höhener et al., 2022). Isotopic data within commercial formulations are sparse but notably highlighted by a pioneering study examining the isotopic signatures of HCH across diverse commercial formulations (Ivdra et al., 2017). While various approaches enable the determination of primary isotopic signatures of point-source legacy contaminants (i.e., hydrocarbons, VOCs) in groundwater (Hunkeler et al., 2008), the nature of diffuse sources for pesticides usually hinders direct field measurements of the pesticide active substance in source commercial formulations. This constraint remains a challenge, with exceptions limited to studies conducted within small catchment areas and over relatively short time frames, typically spanning a few months, and involving detailed farmer surveys concerning the used pesticide formulations (Alvarez-Zaldívar et al., 2018; Höhener et al., 2022; Masbou et al., 2023).

Pesticide formulations typically consist of one or more active substances, which are agrochemicals formulated for pest control purposes. These formulations also incorporate diverse auxiliary components, including solvents, emulsifiers, surfactants, stabilizers, adjuvants, or inert ingredients. These additional elements aid in the delivery, blending, and stabilization of the active substances (Cross and Scher, 1989). Therefore, it is necessary to first extract the active substance from the pesticide formulation for a specific evaluation of its isotope composition using CSIA. Several extraction methods for conducting CSIA of pesticide active substances from environmental samples have undergone testing and validation (Gilevska et al., 2022). However, extraction methods for accurate CSIA measurements of the isotope composition of pesticide active substances from commercial formulations have not been validated yet.

The aim of this study was to evaluate and compare the stable isotope composition variations of active substances in pesticide formulations to determine the suitability of CSIA in identifying the sources or transformation of pesticide residues in the environment. We established a publicly accessible database named ISOTOPEST, dedicated to cataloguing and disseminating typical source isotopic signatures of pesticides. This initiative aims to encourage broader utilization of pesticide CSIA within the scientific community. In this study, we implemented the ISOTOPEST database with the collection of 120 commercial pesticide formulations derived from 23 different manufacturers, along with 25 analytical standards. Our study involved a pesticide formulation extraction validation and the detailed examination of both $\delta^{13}C$ and $\delta^{15}N$ CSIA of 59 formulations and 25 standards, complemented by comprehensive curation of existing literature data.

## 2. Materials and methods

### 2.1. Collection of pesticide commercial formulations

A total of 120 commercial formulations originating from 23 distinct manufacturers were obtained in volumes ranging from 10 to 50 mL, or 10–50 g for powdered variants. These samples were acquired from the Agricultural and Viticulture College of Rouffach (EPLEFPA Les Sillons de Haute Alsace Rouffach), the experimental farm of Epoisses (U2E, INRAE, Bretenière), and an agricultural counter (Comptoir Agricole, Alsace, France). Whenever possible, lot and batch numbers and expiry dates were documented. The aliquots were carefully stored in glass or polypropylene vials at a temperature of 4 °C in a light-free environment at the Earth & Environment Institute (ITES, Strasbourg, France).

### 2.2. Chemicals and solution preparation

Pesticide standards (PESTANAL, purity: >97%), metolachlor-d11 (analytical grade purity, >97%), atrazine-d5 (analytical grade purity, >97%) and solvents (acetonitrile ACN, ethyl acetate EtOAc; HPLC grade purity, >99.9%) were purchased from Sigma–Aldrich. For additional calibration standard preparation and reproducibility checks, stock solutions of pesticides at 1 g $L^{-1}$ were prepared in acetonitrile (ACN) and stored at −18 °C until analysis. Commercial formulations were initially dissolved or diluted, if liquid, in distilled water (>18 MΩ), targeting final aqueous concentrations of 0.3–0.5 g $L^{-1}$ of active molecules. These initial aqueous solutions (M1) were stored in the dark at 4 °C and extracted within 3 days.

### 2.3. Pesticide extraction from commercial formulations

The main extraction method consisted in a liquid-liquid extraction (LLE). Briefly, 1 mL of initial M1 solution was diluted with 4 mL of distilled water in 15 mL centrifuge tubes (Falcon, VWR®). The extraction step consisted of adding 3 mL of EtOAc before vortexing for 1 min and 5 min of ultrasonic bath (Branson 5510, 40 kHz). Depending on the emulsion amount, the tubes were then centrifuged at 5000 rpm for 3–20 min until complete phase separation. The supernatant was transferred to an amber glass vial, and the extraction method was repeated two more times. The obtained extracts were then pooled and concentrated at 20 °C under a gentle $N_2$ stream to the last drop.

For cross-method comparison purposes, five pesticide formulations were also extracted by solid-phase extraction (SPE) technique, as previously described (Gilevska et al., 2022). Briefly, 1 mL of M1 solution was diluted to 100 mL of distilled water and extracted using 1 g of sorbent (SolEx C18, Dionex®). After 20 min of cartridge drying under $N_2$, elution steps consisted of subsequent addition of 5 mL of EtOAc and 5 mL of ACN recovered in an amber glass vial. This solvent mixture was then evaporated under a gentle $N_2$ stream until the last drop.

For both extraction methods, pesticide residues were then resuspended in ACN to a volume of 1 mL by vortexing (5 s) and ultrasonication (5 min). The final solutions (M2), obtained by liquid-liquid extraction and SPE methods, ranged 0.3–0.5 g $L^{-1}$ of active molecules in ACN and were stored in the dark at 4 °C until quantification and pesticide CSIA.

### 2.4. Active substances quantification

Pesticides were analyzed with a gas chromatograph (GC, Trace 1300, ThermoFisher Scientific) coupled to a mass spectrometer (MS, ISQ™, ThermoFisher Scientific). Chromatographic separation was performed with a TG –5MS column (30 m × 0.25 mm ID, 0.25 μ film thickness). S-metolachlor-d11 or atrazine-d5 internal standards were prepared at 300 μg $L^{-1}$ in ACN and injected with every injection to account for analytical bias. Analytical parameters are detailed in (Masbou et al., 2018a). Compound-specific calibration curves were prepared in ACN using corresponding analytical standards (PESTANAL grade). Subsequently, all samples were diluted with ACN to fall within the linear calibration range (10–500 μg $L^{-1}$).

### 2.5. Carbon and nitrogen CSIA of pesticides

Carbon and nitrogen stable isotope signatures of pesticides were measured using a previously described method (Gilevska et al., 2022). Briefly, GC-C-IRMS system consisted in a TRACE™ Ultra Gas Chromatograph (ThermoFisher Scientific) coupled via a GC IsoLink/Conflow IV interface to an isotope ratio mass spectrometer (DeltaVplus, ThermoFisher Scientific). Chromatographic separation was performed on a TG–5MS column (60 m × 0.25 mm ID, 0.25 μ film thickness). Samples were injected in split/splitless modes with an injection volume of 0.5–2 μL and an injector temperature of 250 °C. Samples were injected in triplicate and values were reported as the arithmetic mean. For both elements, target compounds were combusted to $CO_2$ or $N_2$ in a single combined reactor (P/N 1,255,321, NiO tube and CuO–NiO–Pt wires, Thermo-Fischer Scientific) at 1000 °C. For N, a liquid $N_2$ bath was used after the combustion reactor for cryogenic trapping of $CO_2$.

Isotope values of pesticide standards were calibrated relative to Vienna Pee Dee Belemnite (VPDB, carbon) and AIR (nitrogen) scales with an Elemental Analyzer-Isotope Ratio Mass Spectrometry (EA–IRMS) (Flash EA IsoLinkTM CN IRMS, Thermo-Fisher Scientific) using a three-point calibration with international reference materials AIEA600, USGS40, and USGS41. Laboratory BTEX (benzene, toluene, ethylbenzene and o-xylene, carbon) and certified IAEA-600 (caffeine, nitrogen) standards were measured before and during each session to verify the overall performance of the instrument. Standards were measured at least every six samples for carbon and every three samples for nitrogen to monitor measurement accuracy throughout the sequences. The reproducibility of $\delta^{13}C$ and $\delta^{15}N$ measurements was typically <0.5 ‰, while the total uncertainty, including accuracy and reproducibility, was <0.8 ‰. All isotopic measurements of element E (C and N) are reported in delta notation:

$$\delta^{h}E = 1000 \times \left(\frac{R_{sample}}{R_{standard}} - 1\right) \quad (1)$$

where $\delta^{h}E$ is expressed in per thousand (‰) and R refers to the ratio of heavy (h) to light (l) isotopes of the element E ($^{h}E/^{l}E$) in the analyzed samples and the international standards.

### 2.6. Inter-laboratory comparison of pesticide CSIA from analytical standards and commercial formulations

Selected pesticide formulations and corresponding analytical standards were analyzed for carbon CSIA at ITES and at the Laboratoire Chimie Environnement (LCE, Marseille, France). GC-C-IRMS system at LCE laboratory consisted in a TRACE™ GC 1310 (ThermoFisher Scientific) coupled via a GC IsoLink/Conflow IV interface to an isotope ratio mass spectrometer (DeltaV Advantage, ThermoFisher Scientific). Chromatographic separation was performed on a TG–5MS column (60 m × 0.25 mm ID, 0.25 μ film thickness). Samples were injected in split/splitless modes with an injection volume of 0.5–2 μL and an injector temperature of 250 °C. A comparable analytical procedure to that of the ITES laboratory was adhered to, involving the routine injection of in-house alkane standards (carbon CSIA) instead of BTEX. The inter-laboratory comparison was conducted on five pesticides, i.e., S-metolachlor, metalaxyl, metazachlor, tetraconazole, and chlordecone, utilizing a "blind" approach. Both extraction methods (LLE and SPE) were tested for S-metolachlor, metalaxyl and tetraconazole commercial formulations during this exercise.

### 2.7. Statistical analysis

Statistical analyses and boxplot representations were carried out using JMP software (SAS Institute, USA). One-way ANOVA was performed to compare data sets. Homogeneity of variances was tested using the Brown-Forsythe test. In the case of unequal variances, a Welch ANOVA test was used.

The boxplots-derived method was used to exclude outliers. The interquartile range (IQR) is the spread of the middle 50% of the data (25th–75th percentile or first to third quartile). Data excluded from the IQR x 1.5 ranges were considered as outliers. All data are displayed as the mean ± 95% Confidence Interval (CI) unless otherwise specified.

## 3. Results and discussion

### 3.1. Validation of extraction methods for pesticide CSIA from commercial pesticide formulations

The effect of extraction methods on the stable isotope composition of pesticides was examined using five distinct molecules characterized by varying physico-chemical properties (with log$K_{ow}$ values ranging from 1.7 to 3.6) and representing distinct chemical families: chloroacetanilides (S-metolachlor), phenylamides (metalaxyl), triazoles (tetraconazole), strobilurines (kresoxim-methyl), and cinnamic acids (dimethomorph). The extraction recoveries obtained from both LEE and SPE methods, applied to analytical standards and commercial formulations, consistently exceeded 79% for all molecules, formulations, and methodologies (Table 1). This held true across different formulation types (granules, liquids, emulsions) and supplementary adjuvant additions, indicating robust and comparable extraction efficiencies.

The carbon isotopic compositions ($\delta^{13}C$) of the pesticide analytical standards demonstrated insignificant change ($\Delta^{13}C < 0.5$ ‰) between direct analysis and post-extraction processes. This indicates that both LLE and SPE methods did not significantly affect the isotope composition of pesticides in commercial formulations. Nevertheless, this could not be confirmed by direct EA-IRMS measurements on pesticides within commercial formulations due to their diluted nature (e.g., 5% of metalaxyl in BASF Ridgold) and impurities in the formulation.

Taking into consideration the analytical uncertainties, the $\delta^{13}C$ of pesticides after LLE or SPE did not exhibit significant differences, with $\Delta^{13}C_{LLE\text{-}SPE}$ (i.e., $\delta^{13}C_{LLE}$ - $\delta^{13}C_{SPE}$) = 0.0 ± 0.3 ‰ (n = 12, Table 1). For both extraction methods, the GC-IRMS chromatograms, including backgrounds and peak width, were similar (data not shown). The $\delta^{15}N$ values of selected formulations containing S-metolachlor (Mercantor Gold) and tetraconazole (BASF Stroby DF) exhibited insignificant variation across the two extraction methods ($\Delta^{15}N < 0.5$ ‰; data not shown).

The LLE method ease of implementation, cost-effectiveness, and consistent high recovery rates, devoid of carbon isotopic fractionation across various pesticide families, prompted its continued utilization in this study.

### 3.2. The ISOTOPEST database

The ISOTOPEST database includes i) 127 isotope compositions produced in this study, with over 70% derived from commercial formulations and ii) 545 isotope compositions, with over 85% derived from analytical standards, compiled from 57 publications (Höhener et al., 2022). The database consolidates 672 isotope compositions encompassing $\delta^{13}C$, $\delta^{15}N$, $\delta^{37}Cl$, and $\delta^{2}H$ data associated with 452 pesticide commercial formulations and analytical standards (Table 2). Notably, among the pesticide formulations analyzed, the prevalence of analytical standards (n = 344) surpassed that of commercial pesticide formulations (n = 108). This discrepancy mirrors the predominance of analytical pesticide standards utilized in laboratory-based pesticide CSIA. Within this database, the highest representation was observed for analytical standards active substances entering in the composition of insecticides, encompassing 226 isotope compositions, of which 198 were $\delta^{13}C$ values. This emphasis reflects the focus on studies involving hexachlorocyclohexane (HCH) isomers through CSIA (Zhang et al., 2014; Bashir et al., 2015; Ivdra et al., 2017; Liu et al., 2020). In terms of representation, the quantities of active substances possessing insecticidal properties (n = 37) and herbicidal properties (n = 43) were comparable. However, compounds exhibiting fungicidal properties (n = 21 molecules) constituted a relatively smaller proportion within the database, reflecting the typical underrepresentation of this often overlooked category of pesticides (Zubrod et al., 2019).

The $\delta^{13}C$ values were more prevalent (409 entries) than $\delta^{15}N$ values (111 entries). Indeed, the measurement of low pesticide residues concentrations in the environment, the elemental critical mass necessary for reliable CSIA, and the significant contribution (≥50%) of carbon to the overall mass of pesticide molecules have historically constrained CSIA measurements to carbon analysis. Enhanced methodologies, exemplified by the combined oxidation-reduction packed oven for nitrogen and the chromium-based oven for hydrogen (Renpenning et al., 2015), the Gas

**Table 1**
Extraction recoveries and $\delta^{13}C$ of pesticide analytical standards and commercial formulations with liquid-liquid extraction (LLE) and solid-phase extraction (SPE) methods. The uncertainties in $\delta^{13}C$ and recoveries are ascertained through triplicate measurements of a single extraction, and the reported values are indicative of the 2σ level. The uncertainties related to $\Delta^{13}C$ are calculated using error propagation rules, and the reported uncertainties are also presented at the 2σ level. A grey background is employed to emphasize analytical standards.

| Active pesticide substance | Formulation | Content (active substance) | EA-IRMS | GC-IRMS after LLE | | GC-IRMS after SPE | | LLE vs. SPE |
|---|---|---|---|---|---|---|---|---|
| | | | $\delta^{13}C$ (‰) | Recovery (%) | $\delta^{13}C$ (‰) | Recovery (%) | $\delta^{13}C$ (‰) | $\Delta^{13}C_{LLE\text{-}SPE}$ (‰) |
| | Sigma Aldrich PESTANAL | >97% | −30.6 ± 0.6 | 92 ± 4 | −30.7 ± 0.3 | 91 ± 7 | −30.4 ± 0.4 | 0.3 ± 0.5 |
| S-metolachlor | Syngenta Mercantor Gold | 960 g $L^{-1}$ | – | 79 ± 10 | −31.6 ± 0.4 | 89 ± 8 | −32.2 ± 0.5 | 0.6 ± 0.7 |
| | Syngenta Dual Gold | 915 g $L^{-1}$ | – | 91 ± 2 | −31.9 ± 0.4 | 95 ± 7 | −31.8 ± 0.4 | 0.1 ± 0.6 |
| Metalaxyl | Sigma Aldrich PESTANAL | >97% | −31.5 ± 0.1 | 95 ± 10 | −31.7 ± 0.3 | 105 ± 7 | −31.8 ± 0.3 | −0.1 ± 0.5 |
| | BASF Ridgold | 5 % | – | 90 ± 5 | −29.5 ± 0.2 | 92 ± 4 | −29.5 ± 0.3 | 0 ± 0.4 |
| Tetraconazole | Sigma Aldrich PESTANAL | >97% | −31.8 ± 0.1 | 92 ± 5 | −31.8 ± 0.5 | 95 ± 7 | −31.9 ± 0.4 | −0.1 ± 0.7 |
| | Phyteurop Barreur | 100 g $L^{-1}$ | – | 90 ± 6 | −31.4 ± 0.3 | 92 ± 2 | −31.8 ± 0.2 | −0.4 ± 0.4 |
| | Phyteurop Greman | 100 g $L^{-1}$ | – | 101 ± 2 | −34.2 ± 0.2 | 95 ± 7 | −34.3 ± 0.1 | −0.1 ± 0.3 |
| Kresoxim-methyl | Sigma Aldrich PESTANAL | >97% | −28.5 ± 0.1 | 88 ± 4 | −28.0 ± 0.4 | 92 ± 4 | −28.1 ± 0.5 | −0.1 ± 0.7 |
| | BASF Stroby DF | 500 g $kg^{-1}$ | – | 90 ± 6 | −28.3 ± 0.2 | 95 ± 6 | −28.4 ± 0.1 | −0.1 ± 0.3 |
| Dimethomorph | Sigma Aldrich PESTANAL | >97% | −33.2 ± 0.2 | 88 ± 10 | −33.0 ± 0.4 | 95 ± 5 | −33.4 ± 0.5 | −0.4 ± 0.7 |
| | BASF GripTop | 90 g $kg^{-1}$ | – | 86 ± 8 | −32.9 ± 0.2 | 92 ± 9 | −33.0 ± 0.2 | −0.1 ± 0.3 |

**Table 2**
Overview of the ISOTOPEST database encompassing both literature-derived and newly acquired isotope data (update: February 13th, 2024).

| | Commercial formulations | | | | Analytical standards | | | | $n_{molecule\ total}$ [a] |
|---|---|---|---|---|---|---|---|---|---|
| | $n_{formulations}$ | $n_{molecule}$ | $n_C^{13}$ | $n_N^{15}$ | $n_{standards}$ | $n_{molecule}$ | $n_C^{13}$ | $n_N^{15}$ | |
| Fungicides | 40 | 15 | 40 | 19 | 19 | 13 | 19 | 5 | 21 |
| Herbicides | 47 | 8 | 47 | 36 | 99 | 34 | 96 | 46 | 37 |
| Insecticides | 21 | 6 | 21 | 0 | 226 | 41 | 186 | 5 | 43 |
| *Total* | *108* | *29* | *108* | *55* | *344* | *88* | *301* | *56* | *101* |

[a] $n_{molecule\ total}$ corresponds to the number of different molecules in the database within pesticide classes (fungicides, herbicides, insecticides).

Chromatography-Mass Spectrometry (GC-MS) (Ponsin et al., 2019) or liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) techniques (Prieto-Espinoza et al., 2023) for chlorine, have facilitated the expansion of multi-element CSIA (ME-CSIA) for pesticide analysis (Höhener et al., 2022). The ISOTOPEST database stands to gain from these advancements and should progressively be augmented with isotopic data obtained through ME-CSIA measurements.

### 3.3. Stable isotope compositions of pesticides

The carbon and nitrogen isotope compositions of both analytical standards and commercial formulations exhibited slight variations across the various pesticide categories (Fig. 1). Excluding statistical outliers (see Material and Method section), the $\delta^{13}C$ values systematically ranged from −25 to −35 ‰ across all pesticide categories. In average, the fungicide isotope compositions were depleted in $^{13}C$ ($\delta^{13}C = -30.8 \pm 3.1$ ‰, n = 19 analytical standards), which significantly differed ($p < 0.01$) from those of herbicides ($\delta^{13}C = -28.6 \pm 3.1$ ‰; n = 96) and insecticides ($\delta^{13}C = -28.9 \pm 5.4$ ‰, n = 186). The $\delta^{13}C$ values of fungicide and insecticide in commercial formulations did not significantly differ ($p > 0.4$) from those of analytical standards. In contrast, $\delta^{13}C$ values of herbicides in commercial formulations ($-30.3 \pm 0.8$ ‰, n = 47) were significantly lower ($p < 0.001$) than those in analytical standards ($-28.6 \pm 0.6$ ‰, n = 96).

Excluding statistical outliers, the nitrogen isotope composition ($\delta^{15}N$) ranged from −13 to 3 ‰ across all categories. As for carbon, $\delta^{15}N$ values of herbicides in analytical standards ($-3.6 \pm 2.3$, n =46), were significantly different ($p < 0.001$) than those in commercial formulations ($+0.1 \pm 0.5$ ‰, n = 36). However, unlike the carbon dataset, the varying number of $\delta^{15}N$ data within pesticide categories, ranging from n = 0 to n = 46, prevented the possibility of conducting a robust statistical analysis.

As chlorine and hydrogen isotopic datasets are more sparse, they were not included in the statistics and in Fig. 1 (available in the SI, Figure S-1). $\delta^{37}Cl$ values range −5 to 5 ‰ (excluding statistical outliers) and average $-1.5 \pm 0.8$ ‰ (n = 48) and $-0.5 \pm 1.8$ ‰ (n = 12) in the insecticide and herbicide analytical standards respectively. $\delta^{2}H$ values, excluding statistical outliers, ranged from −132 to −46 ‰ and averaged $-84 \pm 10$ ‰ (n = 57) in the insecticide analytical standards.

Overall, the isotopic dataset encompassing carbon, nitrogen, and chlorine exhibited variability within approximately 10 ‰ across distinct pesticide categories, spanning both analytical standards and commercial formulations. This range proves substantial in contrast to the typical stable isotope fractionation observed in the field, for instance, $\Delta^{13}C_{max} \sim 4$ ‰ ($\delta^{13}C_{PIS} - \delta^{13}C_{water}$) for S-metolachlor, a commonly employed chloroacetanilide herbicide (Alvarez-Zaldívar et al., 2018). Therefore, a comprehensive assessment of the stable isotope compositions of individual pesticide molecules in commercial formulations is required to evaluate their sources or degradation employing CSIA in field studies.

### 3.4. Carbon and nitrogen isotope compositions of pesticides in commercial formulations

The carbon and nitrogen isotopic composition of selected pesticide formulations exhibited significant variation (Fig. 2). For instance, significantly distinct $\delta^{15}N$ and $\delta^{13}C$ values were observed in S-metolachlor between analytical standards and the commercial formulations ($p < 0.01$). Discrepancies in these values may be attributable to purification procedures or the source materials used in synthesis, as identified in prior forensic investigations (Benson et al., 2006). However, $\delta^{13}C$ ($-32.1 \pm 0.6$ ‰, n = 4) and $\delta^{15}N$ ($+2.2 \pm 0.5$ ‰, n = 4) values in four main commercial formulations containing S-metolachlor were similar among different manufacturers (Syngenta: Mercantor Gold, Dual Gold Safeneur, Camix 440; Phyteurop: S-Metolastar). Therefore, consensus means of $\delta^{13}C = -32.1 \pm 0.6$ ‰ (n = 4) and $\delta^{15}N = +2.2 \pm 0.5$ ‰ (n =

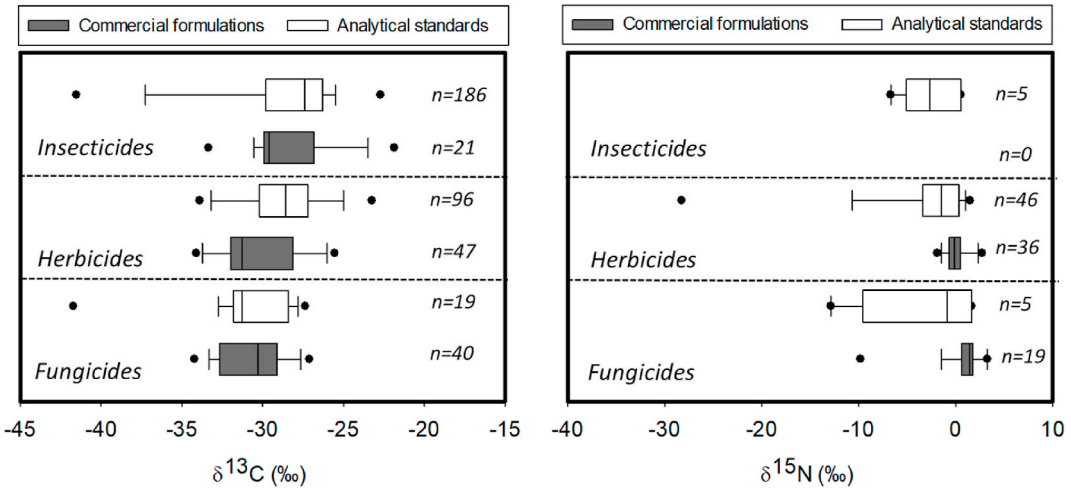


**Fig. 1.** Carbon ($\delta^{13}C$, left) and nitrogen ($\delta^{15}N$, right) stable isotope composition for individual pesticide classes (insecticides, herbicides and fungicides) and formulation categories (analytical standards and commercial formulations). The boxplots display the median (bold line), first and third quartiles (left and right end of box) and the 1.5-fold interquartile range (error bars). Outliers are indicated with black dots.

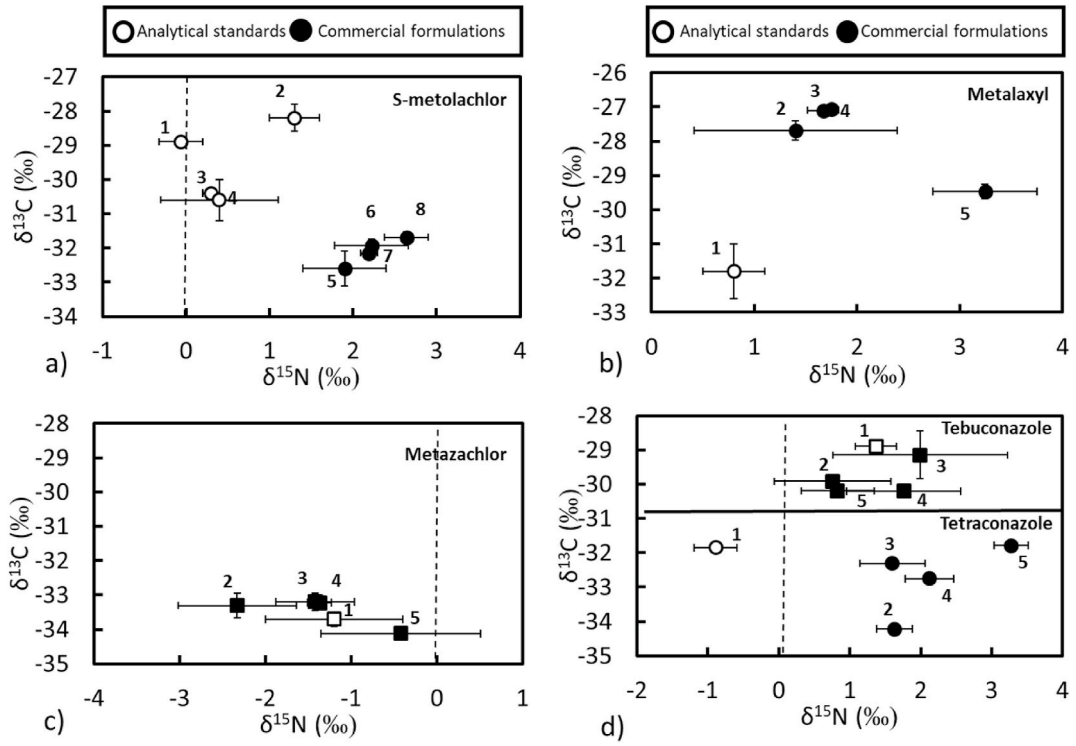


**Fig. 2.** Dual plots of $\delta^{13}C$ and $\delta^{15}N$ values for analytical standards and commercial formulations containing (a) S-metolachlor, (b) metalaxyl, (c) metazachlor, (d) tebuconazol and tetraconazole active molecules. All measurements were conducted exclusively at Lab 1, unless otherwise specified. Numbers correspond to the following formulations.
S-metolachlor: 1: Toronto Research, 2: Chemos (Torrentó et al., 2019), 3: Oskar Tropitzsch (Torrentó et al., 2021), 4: Sigma Aldrich (Masbou et al., 2018a), 5: Syngenta Mercantor Gold*, 6: Syngenta Dual Gold Safeneur, 7: Phyteurop S-Metolastar, 8: Syngenta Camix 440.
Metalaxyl: 1: Sigma Aldrich (Masbou et al., 2018b), 2: Syngenta Folio Gold 536.3 SC, 3: Syngenta Santhal, 4: Syngenta Bion mx 42.76 WG, 5: Syngenta Ridgold F.
Metazachlor: 1: Sigma Aldrich, 2: BASF Novall, 3: BASF Butisan S, 4: GlobalChem Rapsan TDI, 5: BASF Alabama.
Tebuconazole: 1: Sigma Aldrich, 2: Bayer Abilis, 3: Phyteurop Balmora, 4: Bayer Nativo, 5: Nufarm Epopee EC.
Tetraconazole: 1: Sigma Aldrich, 2: Phyteurop Greman, 3: Phyteurop Timbal EW, 4: Philagro Lidal, 5: Phyteurop Barreur.

4) can be considered as the reference primary isotope signature for S-metolachlor. This underscores the potential of S-metolachlor CSIA to assess transformation processes involving molecular bound cleavage rather than to distinguish sources in field studies. Notably, four commercial formulations of S-metolachlor currently represent over 80% of the formulations sold in France in 2021 (refer to SI). Therefore, the consensus mean of isotopic compositions could be utilized for evaluating S-metolachlor degradation in the field without necessitating a systematic characterization of the commercial formulation applied in the study area.

Metazachlor, another widely used herbicide, had similar carbon isotope signatures in analytical standards ($\delta^{13}C = -33.7 \pm 0.2$ ‰, n = 1) and commercial formulations ($\delta^{13}C = -33.5 \pm 0.4$ ‰, n = 4), while $\delta^{15}N$ ranged from −0.4 ‰ to −2.3 ‰. The four formulations containing metazachlor in the database accounted for more than 50% of the metazachlor sold in France in 2021 (active substance masses, see SI for details). Therefore, the consensus means of $\delta^{13}C = -33.5 \pm 0.4$ ‰ (n = 4) for metazachlor may be used as a preliminary estimate of carbon primary isotope signature in field studies.

For tetraconazole, a triazole fungicide, commercial formulations exhibit more negative and sparser $\delta^{13}C$ compared to tebuconazole analytical standard. However, the two formulations from ISAGRO SPA manufacturer, commonly used in France (73% of tetraconazole sold in 2021), exhibited similar carbon ($\delta^{13}C = -32.5 \pm 0.4$ ‰, n = 2) and nitrogen ($\delta^{15}N = 1.9 \pm 0.5$ ‰, n = 2) isotope compositions, which may be cautiously used in field studies. For tebuconazole triazole fungicide, $\delta^{13}C$ and $\delta^{15}N$ values were also found within a narrow range (1 ‰) in commercial formulations, allowing to derive consensus means of $\delta^{13}C = -29.9 \pm 0.5$ ‰ (n = 4) and $\delta^{15}N = 1.3 \pm 0.6$ ‰ (n = 4). With a representativity of 3% of the total tebuconazole sold in France in 2021 (see Supplementary Information for details), the dataset should be complemented with other formulations to obtain a primary isotope signature that could be more safely utilized in field studies.

Finally, three groups of metalaxyl could be distinguished based on the carbon and nitrogen isotopic compositions: i) the analytical standard ($\delta^{13}C = -31.8 \pm 0.8$ ‰), ii) Folio Gold 536.3 SC, Santhal, and Bion mx 42.76 WG commercial formulations ($\delta^{13}C$ ranging from −27.0 to −27.7 ‰), and iii) Syngenta Ridgold F commercial formulation ($\delta^{13}C = -29.5 \pm 0.2$ ‰). Therefore, no relevant consensus mean could be obtained from these commercial formulations, which represent 27% of applied metalaxyl in France in 2021. Other formulations, such as Syngenta Wakil XL (47% of the applied metalaxyl, France, 2021), may be analyzed in the future to obtain a more representative primary isotope signature of metalaxyl.

Overall, these findings indicate a limited range of carbon and nitrogen stable isotope compositions ($\Delta^{13}C$ and $\Delta^{15}N \sim 2$ ‰) in individual pesticides within commercial formulations. In contrast, significant differences in the $\delta^{13}C$ values were observed within pesticide chemical families. For example, in Phyteurop formulations, the $\delta^{13}C$ values of the triazoles tetraconazole and tebuconazole exhibited a difference of 3 ‰. Additionally, slight variations were observed in the $\delta^{13}C$ values of chloroacetanilides such as S-metolachlor (−32.1 ± 0.6 ‰) and metazachlor (−33.5 ± 0.4 ‰). These findings, observed in pesticide molecules belonging to the same chemical families, underscore the need for a more comprehensive examination of the primary isotope signature of pesticides in commercial formulations, despite assumed similarities in their synthesis routes and the origin of reagents.

### 3.5. Inter-laboratory comparison of pesticide CSIA

The absence of globally certified isotopic standards for pesticides, the diversity of isotopic systems (C, N, Cl, H, S, etc.), and multiple analytical methodologies, including GC-IRMS, GC-MS, LC-MS, Orbitrap, GC-MC-ICPMS, collectively pose a challenge for reliably determining the primary isotope signatures of pesticides in commercial formulations. In this context, the ISOTOPEST database represents a crucial step and a shared platform to promote and facilitate inter-laboratory comparisons. Compound-specific isotope analysis (CSIA) of S-metolachlor, metalaxyl, metazachlor, tetraconazole and chlordecone was conducted as a first inter-laboratory comparison involving ITES and LCE laboratories to determine primary isotope signatures. Primarily, the carbon isotope compositions ($\delta^{13}C$) of distinct commercial formulations and corresponding analytical standards were evaluated in both laboratories.

Despite slight differences in analytical and instrumental conditions (see Material and Methods section), the $\delta^{13}C$ values obtained from both laboratories were comparable (Fig. 3), falling within their respective margins of uncertainty ($|\Delta^{13}C|_{average} = 0.6$ ‰ and $|\Delta^{13}C|_{max} = 1.4$ ‰; see SI). In particular, $\Delta^{13}C_{Lab1\text{-}Lab2}$ did not exceed 0.7 ‰ for S-metolachlor, regardless of the extraction method employed.

The largest shift, with $\Delta^{13}C_{Lab1\text{-}Lab2} = -1.4$ ‰, was observed for chlordecone Sigma Aldrich analytical standard, despite similar results obtained from a secondary analytical standard (Cluzeau, $\Delta^{13}C_{Lab1\text{-}Lab2} = -0.2$ ‰) and an extracted commercial formulation (Curlone, $\Delta^{13}C_{Lab1\text{-}Lab2} = -0.4$ ‰). Both laboratories obtained shifted $\delta^{13}C$ values from EA-IRMS measurements, yielding $\delta^{13}C = -26.8 \pm 0.1$ ‰ and $\delta^{13}C = -26.4 \pm 0.5$ ‰ for the Sigma Aldrich and Cluzeau analytical standards, respectively. A previous study has documented a comparable isotopic shift likely arising from the incomplete $CO_2$ conversion of chlordecone within the GC-IRMS combustion reactor (Chevallier et al., 2018).

### 3.6. Storage and banking of pesticide commercial formulations

The present study has established a public pesticide database, encompassing the storage of 120 commercial pesticide formulations, to facilitate the reliable determination of primary isotope signatures in future research. This database allows for additional stable isotope measurements using alternative instruments and set-ups, notably for chlorine, hydrogen and sulfur CSIA, and position-specific isotope analysis. Furthermore, the long-term storage of commercial pesticide formulations ensures their availability for future investigations. Due to the susceptibility of pesticides to bio- and photo-degradation, all formulations (liquid, emulsion, and granular) were preserved at 4 °C in the dark.

Pesticides in various commercial formulations did not undergo significant degradation (<5%, data not shown), and carbon isotope compositions ($\Delta^{13}C_{after\text{-}before\ storage} < 0.5$‰) remained unchanged after 4–5 years of storage (Fig. 4). The six selected formulations included emulsifiable concentrate, granular, and emulsion types, providing a representative panel of existing pesticide formulations. Notably, despite surpassing the recommended expiration dates (February 2021 for Syngenta Mercantor Gold and February 2020 for Dow Agroscience Systhane), these commercial formulations were stable in terms of both the concentration and the isotopic composition of active molecules. This suggests the presence of stabilizing agents or adjuvants within commercial formulations, preserving pesticide stability over time (Zhang et al., 2023).

The results indicate that the storage conditions of the database may be deemed suitable for long-term preservation of pesticide formulations for future isotopic analyses. We plan to extract the five pesticides from commercial formulations every 5–10 years to follow-up potential changes in both their concentration and stable isotope composition.

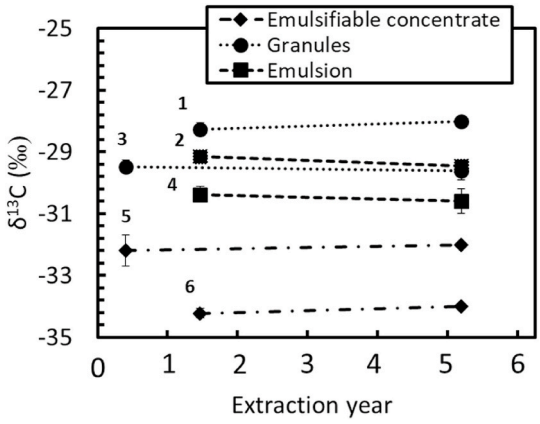


**Fig. 4.** Effect of storage duration on carbon isotope composition ($\delta^{13}C$) of pesticides in commercial formulations. Numbers correspond to the following formulations: 1: BASF Stroby DF (kresoxim-methyl), 2: Phyteurop Balmora (tebuconazole), 3: Syngenta Ridgold F (metalaxyl), 4: Corteva Agriscience Systhane (myclobutanil), 5: Syngenta Mercantor Gold (S-metolachlor) and 6: Phyteurop Greman (tetraconazole).

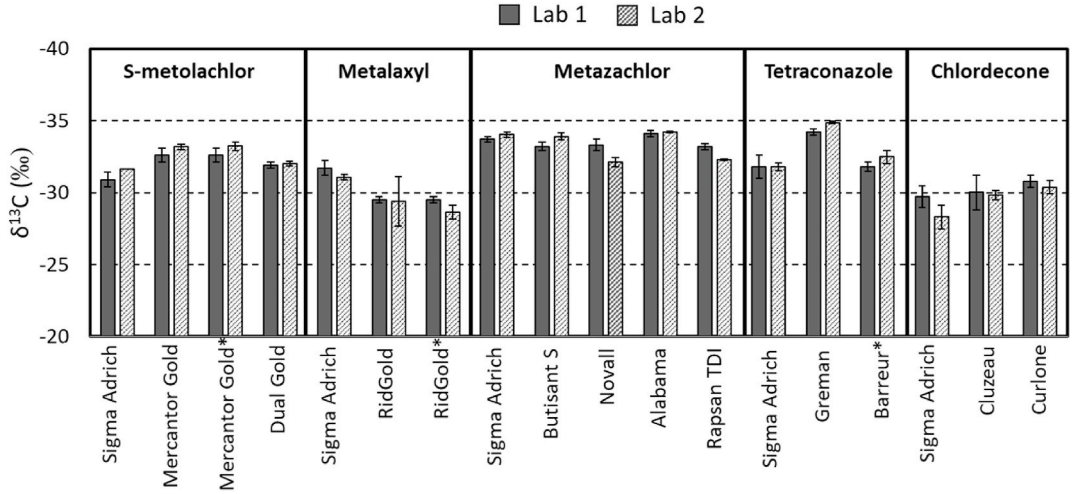


**Fig. 3.** Comparison of $\delta^{13}C$ obtained in Laboratory 1 and Laboratory 2 for active molecules of S-metolachlor, metalaxyl, metazachlor, tetraconazole and chlordecone derived from analytical standards and commercial formulations. All commercial formulations were extracted using the liquid-liquid extraction method, except for those denoted by an asterisk (*) which underwent extraction through solid-phase extraction techniques.

## 4. Conclusions

The public ISOTOPEST database, accessible at https://ites.unistra.fr/isotopest, stands as a valuable resource for ongoing research requiring the isotope composition of pesticides in both analytical standards and commercial formulation. The current composition of the database predominantly consists of commercial formulations from European manufacturers. However, for the broader application of the pesticide CSIA approach, contributions from other global regions will be necessary. The transparency and comprehensive extraction, analysis and validation procedures provided on the website ensure reliable utilization and enable comparisons across studies. The database holds particular promise for identifying the primary isotope signatures of pesticides in commercial formulation during field studies, addressing current challenges associated with limited access to these formulations. Given the relatively narrow range of carbon and nitrogen isotope signature within formulations for a single pesticide, the application of CSIA emerges as a powerful tool for unravelling transformation processes and pathways rather than merely tracing pesticide sources in field studies.

Anticipating future advancements in analytical methodologies, the ISOTOPEST database is poised to accompany the evolution towards multi-element CSIA, incorporating stable isotope signatures of different elements, beyond carbon, of pesticides in standards and commercial formulations. The comprehensive protocol outlining the analytical prerequisites for contribution is extensively expounded upon in the ISOTOPEST website, specifically within the designated section titled “How to Contribute”. This expansion will enhance the database utility, complementing the well-documented carbon isotopic compositions. It is crucial to acknowledge that the isotopic composition of individual pesticides in commercial formulations may undergo changes over time and across different lot or batch numbers due to potential modifications introduced by manufacturers in the formulation, reagents, or synthesis processes. The associated challenge lies in obtaining this evolving information, underscoring the significance of maintaining regular updates through the analysis of pesticide isotope compositions in new formulations. This proactive approach is essential to ensure the continued relevance and accuracy of the ISOTOPEST database in advancing the field of pesticide isotope analysis.

## CRediT authorship contribution statement

**Jérémy Masbou:** Writing – original draft. **Patrick Höhener:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Sylvain Payraudeau:** Writing – review & editing, Conceptualization. **Fabrice Martin-Laurent:** Writing – review & editing, Conceptualization. **Gwenaël Imfeld:** Writing – original draft, Visualization, Validation, Resources, Project administration, Formal analysis, Data curation, Conceptualization.

## 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.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2024.141488.

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