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# Isotopic Fingerprinting for the Authenticity Control of Crop Protection Active Compounds using the Representative Insecticide Fipronil

Philipp Weller,*[,†] Markus Boner,[§] Hilmar Foerstel,[§] Horst Becker,[†] Benjamin Peikert,[†] and Wolfgang Dreher[†]

[†]BASF SE, Agricultural Solutions, APE/MB, Speyerer Strasse 2, 67117 Limburgerhof, Germany

[§]TÜV Rheinland Agroisolab GmbH, TÜV Rheinland-Gruppe, Germany

**ABSTRACT:** Isotopic fingerprinting was evaluated for its potential to generate characteristic fingerprints of crop protection products in an extensive survey, using the insecticide Fipronil. One hundred and twenty batches of Fipronil from the BASF production site in France were analyzed for the isotope ratios of $\delta^{13}C$, $\delta^{15}N$, and $\delta^{34}S$. Samples spanned a production time of four years and were analyzed by elemental analysis, coupled to isotope ratio mass spectrometry (EA/IRMS). A number of Fipronil samples from other sources were analyzed in the same manner and were compared to the samples from BASF by means of multivariate data analysis. The isotopic fingerprint was sufficiently specific to differentiate between Fipronil from BASF production and Fipronil from other producers. This suggests that isotopic fingerprinting is suitable for the authenticity control of active compounds in crop protection products. It is anticipated that this technique will deliver great benefit in the defense against counterfeits and illegal parallel imports.

**KEYWORDS:** Fipronil, IRMS, EA/IRMS, authenticity, crop protection products, illegal parallel imports

## INTRODUCTION

Crop protection products are widely used all over the world and are an integral part of modern agriculture.

Over the past years, these products have become more and more subject to extensive counterfeiting. Advances in technology, as well as less stringent trade laws, facilitate the spread of counterfeit products.

Counterfeit crop protection products can come in various forms: low-quality copies with no or plain labeling, containing unregistered and untested substances, and also as highly sophisticated copies of branded and patent-protected products. More and more, these come with the same labeling and packaging. Illegal parallel imports are another form of fake pesticides, which masquerade as legitimate products but very often contain products of inferior quality or even hazardous chemicals.[1]

The term "parallel import" refers to the fact that an authorization holder for a crop protection product that is authorized in one European Union (EU) member state can apply for a parallel trade permit to place this product on the market of another EU member state. In November 2009, the new Regulation (EC) No. 1107/2009 concerning the placing of plant protection products on the market was published to replace Directive 91/414/EEC, which covers not only the approval but also the trade with such products. It will become fully applicable as of June 14, 2011. This directive establishes that a parallel trade permit will be granted only if the product is identical to a reference product authorized in the importing member state. One of the key elements there is the definition that a product is considered to be identical to the reference product if it was "manufactured by the same company or by an associated undertaking, or under licence in accordance with the same manufacturing process".

This means that a product which does not fulfill these requirements and still is exported to another member state is illegal.

The European Crop Protection Association (ECPA) estimates that 5−7% of Europe's crop protection products are illegal, with an increasing tendency. Illegal pesticides pose a serious threat to farmers' and consumers' health, to the environment, and to farmers' livelihoods. The crop protection industry has a high interest in reducing fake products to the minimum possible, not least because of product liability reasons.

The trade with illegal products often involves criminal activity and therefore supports a black economy in Europe. The market for fake crop protection products in Europe is estimated to 700 million euros and, correspondingly, a loss of tax revenues of 21−30 million euros.[1]

Defense against counterfeit products requires sophisticated analytical techniques that must be capable of delivering unequivocal results, on the one hand, and, on the other hand, robust enough to detect adulterations in products with variable compositions.

One of the most common approaches is the so-called "fingerprinting" of products, usually performed by spectroscopic techniques, such as (N)IR, NMR, or organic MS, often coupled to chromatographic techniques. Typical chemical properties of the product, such as formulation compounds or process-specific impurities, are used to generate a characteristic pattern, similar to a human fingerprint.

However, techniques based on the detection of impurities or byproducts are often not suitable to prove whether an active compound in a product is of authentic origin, as this usually requires knowledge of the source of the active compound. This is especially true for counterfeit products with virtually the same composition as an authentic product, which is more and more the case for illegal parallel imports.

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In this context, isotopic fingerprinting is a very promising analytical technique, as it does not rely on the chemical composition of a product, but uses "atomic imprinted information".

In the field of authenticity analyses via stable isotope ratios, two different techniques are commonly used: site-specific natural isotope fractionation (SNIF) NMR[2,3] and the more extensively used isotope ratio mass spectrometry (IRMS).

IRMS is a mass spectrometry-based technique that has gained significant popularity in recent years.[4−6] This may be, among other reasons, due to the rapid price decrease of the equipment.

In IRMS, the substance of interest is normally converted into simple molecules, such as carbon dioxide or hydrogen, either by elemental analysis or by pyrolysis, which are used to measure the respective isotope ratios.

The stable isotope analysis of light elements (or so-called "bioelements") hydrogen, carbon, nitrogen, oxygen, and sulfur has a long history of over 20 years in food authenticity control, which results in a plethora of application examples.[7,8] Here, the investigations mostly addressed the authenticity of flavors, wine, fruit juices, honey, olive oil, or spirits.[4,9−16]

Much more complex issues, such as the differentiation of origin of meat from conventional or organic farming, can also be addressed successfully.[16,17]

Hence, IRMS is a generally accepted technique for the authenticity control of food products[18,19,23] and is extensively used by the producing industries as well as by governmental institutions.[20−22]

Not only has the food industry discovered the potential of IRMS for authentication purposes, but also the pharmaceutical industry has shown an increased interest in the use of isotopic fingerprinting in recent years.[24−26] Isotope ratios in pharmaceutical active compounds can be used to assess the source of the products and, moreover, the synthetic pathway according to which an active compound was manufactured.[27,28]

As the production of pharmaceutical active ingredients is closely related to the production of crop protection active compounds, it is almost remarkable that information on isotopic fingerprinting of crop protection active compounds, especially in the context of authenticity control, is scarce in the literature. However, isotopic fingerprinting is more and more used to assess the origin and fate of organic compounds in the environment[29] or to evaluate the effectiveness of synthesis processes.[30]

For this reason, compound-specific isotopic fingerprinting was evaluated for its potential in the authenticity control of active compounds used in crop protection products. As an exemplary active, the insecticide Fipronil, which is widely used all over the world in different applications, was chosen.

It is therefore of particular interest to differentiate between different sources and, eventually, differentiate between authentic and nonauthentic products under realistic conditions.

The aim of the study was to evaluate whether a large set of Fipronil production batches (120 representative batches over a period of 4 years) has a sufficiently constant isotopic fingerprint that allows one to identify and furthermore differentiate original products from products of generic producers.

## MATERIALS AND METHODS

**Materials.** Twelve hundred technical grade Fipronil (Figure 1) reference samples from a BASF production site were collected, which spanned a production period from 2005 to 2009. The purity of the material was 98% (w/w) on average. Each sample is representative of one batch. For analysis, 120 of the 1200 samples were selected randomly, but evenly distributed.

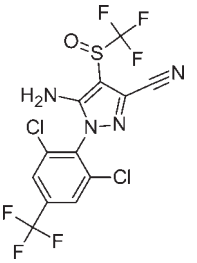


**Figure 1.** Structural formula of Fipronil ($C_{12}H_4Cl_2F_6N_4SO$).

Purified Fipronil (99% w/w) was obtained as a certified reference standard from internal sources and was used for quality control purposes.

Samples of non-BASF Fipronil of technical grade were purchased from various third-party manufacturers.

End-use Fipronil formulations from BASF production were from the last two years and comprised an 80% (w/w) granulate formulation (here referred to as BASF1), a 25% (w/v) suspension concentrate (BASF2), and a 5% (w/v) suspension concentrate (BASF3).

Third-party Fipronil formulations were 25% (w/v) suspension concentrates (Gen_Prod1 and 2) and 5% (w/v) suspension concentrates (Gen_Prod3 and 4).

**HPLC System and Purity Control.** Isolation of Fipronil from end-use products was performed using a Waters LC-Autopurification system, coupled to a Waters 3100 single-quadrupole mass detector and a Waters 2489 UV−vis detector at 230 nm. The column used was a Luna C10, 150 × 21.2 mm, 5 $\mu$m, from Phenomenex and the gradient solvent system was acetonitrile/water and pure acetonitrile. Chromatographic separation was performed using gradient elution. Mobile phase A was 90% water and 10% acetonitrile, with 0.5% formic acid (v/v). Mobile phase B was acetonitrile. The gradient program started at 90% A for 3 min, decreasing to 50% for 1 min, then from 50 to 25% for 10 min, and then to 0% for 0.1 min. Finally, isocratic elution (90% A) followed for 6.9 min. The total run time was 21 min at a mobile phase flow rate of 15 mL/min. Injection volume was 4 mL. Sample preparation was as follows: the products were diluted with 50:50% (v/v) acetonitrile/water to a Fipronil concentration of 1−2.5% (w/v), depending on the type of formulation. After sonication and filtration, the solution was subjected to HPLC separation.

For purity control purposes, an analytical HPLC system, coupled to an ESI-MS/MS detector and UV−vis detection at 230 nm was used. The HPLC system was an Agilent 1100 system, equipped with a binary pump, solvent degasser, column oven, and diode array detector operating at 230 nm. The column used was a Thermo Betasil C18 100 × 2.1 mm, 5 $\mu$m, at a flow of 0.6 mL/min. Mobile phase A was water, and mobile phase B was acetonitrile. All solvents were of LC-MS grade. The gradient program started at 60% A for 1.2 min, decreasing to 45% for 1.6 min, then from 45 to 40% for 2.2 min, and then to 0% for 5 min. Finally, isocratic elution (60% A) followed for 4 min. The total run time was 14 min, and the injection volume was 10 $\mu$L.

The MS/MS detector was an Agilent 6460 triple-quadrupole system, operating in positive and negative full scan mode, and was used for confirmation versus authentic certified reference material of Fipronil.

**IRMS.** Technical grade Fipronil was used after gentle drying in an exsiccator over silica gel. Fipronil from formulations was isolated by use of preparative HPLC, and the purity was controlled by combined detection of UV−vis at 230 nm and mass selective detection. After isolation, the Fipronil solution was flash evaporated to dryness and afterward stored overnight in an exsiccator over silica gel.

Samples of the predried Fipronil were weighed into tin foil containers (~0.3 mg), crimped tight, and were then introduced into elemental analysis. Each sample was measured in triplicate.

The sample molecule is converted into simple gases ($CO_2$, $SO_2$, $N_2$) and reaction water, which, as an unwanted substance, is removed by an inline water trap. The gases are introduced into the isotope ratio mass spectrometer by means of a gas dilution interface (Thermo Scientific ConFlo IV), which dilutes the sample gas with helium. The mass spectrometer measures the isotope ratios of the sample gas relative to a laboratory tank gas, which was, prior to the analysis, referenced against an international standard.

Carbon ($\delta^{13}C$) and nitrogen ($\delta^{15}N$) analyses were performed using a Thermo Fisher Elemental Analyzer coupled to a Delta V Plus Advantage isotope ratio mass spectrometer with a ConFlo IV interface.

Stable isotope ratios of carbon ($\delta^{13}C$) are measured as $CO_2$, whereas ratios of nitrogen ($\delta^{15}N$) are measured as $N_2$.

The furnace temperature of the oxidation reactor was 1020 °C; the reduction furnace was operated at 680 °C. The column (Poropack QS 50/80 mesh, 3 m × 5 mm) was heated to 41 °C.

Sulfur ($\delta^{34}S$) analyses were performed using a Hekatech Eurovector EA Elemental analyzer (Hekatech GmbH, Wegberg, Germany). Sulfur ($\delta^{34}S$) is measured as $SO_2$.

The furnace temperature of the oxidation reactor was 1000 °C; the reduction furnace was operated at 860 °C. The packed column (Hekatech Sulfur 6 × 4, 0.8 m) was heated to 94 °C.

The respective reactors were prepared according to the procedures as described in the EA manuals.

**Reference Materials.** Isotope ratios are typically given in $\delta$ values, which describe the difference of the sample from an international reference standard in per mil. The $\delta$ value is defined as

$$\delta = \frac{R_{\text{sample}}}{R_{\text{reference}}} - 1$$

where $R_{\text{sample}}$ is the respective isotope ratio of the sample material and $R_{\text{reference}}$ corresponds to the ratio of the international reference material. The reference materials were supplied by the International Atomic Energy Agency (IAEA) and were the following: IAEA-CH-7 ($\delta^{13}C = -32.15‰_{VPDB}$), IAEA-N-1 ($\delta^{15}N = 0.4‰_{air\ N}2$), IAEA-S-1 ($\delta^{34}S = -0.3‰_{VCDT}$), IAEA-S-2 ($\delta^{34}S = 22.7‰_{VCDT}$), and IAEA-S-3 ($\delta^{34}S = -32.3‰_{VCDT}$).

$\delta^{13}C$ and $\delta^{15}N$ were calibrated using one-point calibrations; $\delta^{34}S$ was calibrated using three points.

For routine measurement, a secondary reference material was used. This term refers to a commonly available, stable material that is referenced once against the IAEA materials. This indirectly referenced substance is then used for the calibration done on every run. For this purpose, 2,5-bis(5-*tert*-butylbenzoxazol-2-yl)thiophene (BBOT) was used, as it contains every relevant element and is easy to handle, which simplifies the calibration procedure.[31]

The data obtained here are also transferred into a quality control card to monitor potential deviations.

**Data Analysis.** Data obtained from the two quality control cards were also used to estimate the robustness and uncertainty of the measurement.

For the measurement uncertainty $u$, the following equation was used, according to common practice:[32]

$$u = \frac{\text{SD} \times t}{\sqrt{n}}$$

SD is the standard deviation of the respective measurement; $t$ is the Student $t$ factor for $f = 19(n - 1)$ for $P = 95\%$, 2.093; and $n$ is the number of samples. For an estimate of robustness, the relative standard deviation was used.

**Table 1. BBOT Quality Control[a]**

| isotope | mean isotope ratio (‰) | SD (‰) | rel SD (%) | uncertainty $u$, $P = 95\%$ |
|---|---|---|---|---|
| $\delta^{13}C$ | −25.67 | 0.62 | 2.4 | 0.29 |
| $\delta^{15}N$ | −0.28 | 0.08 | 2.9 | 0.04 |
| $\delta^{34}S$ | −8.80 | 0.78 | 8.9 | 0.37 |

[a] Quality controls were performed during routine measurements; $n = 20$.

**Table 2. Fipronil Quality Control[a]**

| isotope | mean isotope ratio (‰) | SD (‰) | rel SD (%) | uncertainty $u$, $P = 95\%$ |
|---|---|---|---|---|
| $\delta^{13}C$ | −32.9 | 1.2 | 3.6 | 0.56 |
| $\delta^{15}N$ | −9.8 | 1.3 | 13.3 | 0.61 |
| $\delta^{34}S$ | 4.1 | 0.7 | 17.1 | 0.33 |

[a] $n = 20$.

Multivariate data analysis, in particular, principal component analysis (PCA), was performed using The Unscrambler V10.0.1 from Camo Software AS.

## RESULTS AND DISCUSSION

**Halogen Influence on Measurement Stability.** In trials prior to the study conducted here, Fipronil was found to be a substance difficult to analyze by elemental analysis. This is especially due to the fact that Fipronil contains 26 atom % of fluorine and 16 atom % of chlorine. Under the given conditions, that is, 1020 °C, organic halogens feature a plethora of different, unwanted reactions that will cause problems in terms of stability of measurement and equipment lifetime.

Therefore, special emphasis was set on the method control system. For this purpose, two substances were used: BBOT, which was already used successfully as a multielement reference,[31] and technical grade Fipronil from a single batch. BBOT was used to assess the status quo of the instrumentation, especially before and after new reactors were inserted. BBOT features easy handling and usually good stability in measurement, which are in principle ideal properties of a reference. However, BBOT does not contain halogens; therefore, it was decided to add Fipronil as a quality control standard to address the effects of fluorine and chlorine.

BBOT measurements were performed within Fipronil sequences and, as a consequence, the stability of analysis was significantly influenced by the Fipronil measurements (Table 1). This resulted in higher standard deviations. It is understood that such high relative standard deviations would usually not be within acceptable ranges, but with respect to the high halogen content in the Fipronil samples, they were considered to be tolerable.

These adverse effects were even stronger when Fipronil was analyzed. Data generated by using purified Fipronil (99% v/v) showed a significant decrease of reproducibility of all of the delta values (Table 2). Furthermore, the overall lifetime of the reactor, which usually has a capacity of ~500 runs for C/N (Thermo EA) and ~250 runs for S (Eurovector EA), was also significantly reduced. A sufficient stability was obtained only up to a maximum of 100 runs in both systems. The Poropack column used in the Eurovector EA had to be replaced after ~500 runs.

**Table 3. Data from BASF Fipronil[a]**

| sample | $\delta^{13}$C mean isotope ratio (‰) | SD (‰) | $\delta^{15}$N mean isotope ratio (‰) | SD (‰) | $\delta^{34}$S mean isotope ratio (‰) | SD (‰) |
|---|---|---|---|---|---|---|
| BASF | −33.5 | 0.6 | −8.6 | 1.1 | 3.5 | 1.1 |
| Gen_1 | −33.7 | 0.1 | −8.2 | 0.1 | −5.5 | 0.1 |
| Gen_2 | −31.9 | 0.1 | −4.0 | 0.1 | −7.1 | 0.2 |
| Gen_3 | −30.3 | 0.2 | −14.6 | 0.3 | −2.5 | 0.3 |
| Gen_4 | −32.7 | 0.1 | −2.5 | 0.1 | −7.1 | 0.2 |
| Gen_5 | −23.4 | 0.1 | −7.9 | 0.1 | 2.0 | 0.1 |
| Gen_6 | −32.5 | 0.1 | −5.7 | 0.1 | −2.0 | 0.2 |

[a] BASF samples: $n$ = 120; other sources: $n$ = 1.

**Table 4. Statistical Data for BASF Fipronil[a]**

| BASF | $\delta^{13}$C (‰) | $\delta^{15}$N (‰) | $\delta^{34}$S (‰) |
|---|---|---|---|
| $n$ | 120 | 120 | 120 |
| minimum | −34.5 | −11.1 | 1.6 |
| first quartile | −33.9 | −9.2 | 2.6 |
| median | −33.5 | −8.6 | 3.9 |
| third quartile | −33.1 | −7.9 | 4.6 |
| maximum | −32.4 | −7.0 | 4.6 |
| span | 2.1 | 4.1 | 3.0 |
| SD | 0.6 | 1.1 | 1.1 |

[a] $n$ = 120 samples.

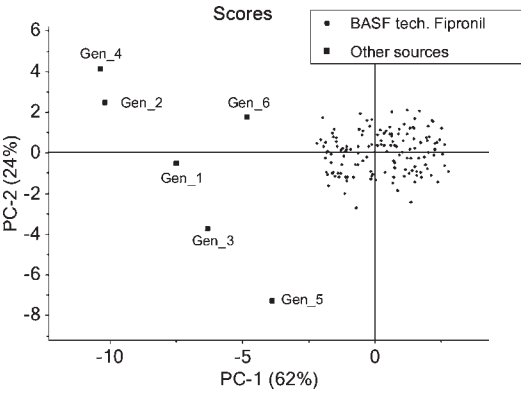


**Figure 2.** PCA of $\delta^{13}$C, $\delta^{15}$N, and $\delta^{34}$S of technical grade Fipronil from BASF production and other sources.

However, even with the reduced stability of the system, it was possible to differentiate different sources of Fipronil, which is shown in the following.

**Fipronil from BASF and Other Sources.** A set of 120 batches of Fipronil, representing 10% of a production time of four years, was analyzed to build a solid database. The relatively high number of samples was used to compensate for variations in the production and also to address the decreased measurement stability.

Table 3 shows the data generated from measurements of technical grade Fipronil from BASF ($n$ = 120). In comparison, data from technical grade Fipronil of different other sources (Gen_1−Gen_6) are also shown. Measurements of these other sources are the average of triplicate measurements. This means, however, that the standard deviations of the delta values generated from the generic products stem from only the measurement, whereas the deviations observed in the BASF samples additionally result from production variations during a period of four years. It is in the nature of authenticity controls that there is usually only one suspicious sample available which has to be compared against a database of known samples, but this underscores the need for a statistically sound data basis that has to cover the relevant production period.

Whereas most of the generic samples show significantly different C/N patterns compared to the BASF Fipronil and are, furthermore, also differentiable from each other, the sample Gen_1 lies within the standard deviation of the data set for BASF. This means that this particular sample of a third-party Fipronil is not differentiable by using only $\delta^{13}$C and $\delta^{15}$N, which underscores the importance of measuring $\delta^{34}$S as a third parameter. Even though the standard deviation of the $\delta^{34}$S measurement is relatively high, the combined data still allow the clear separation of all Fipronil sources.

Table 4 shows the statistical data calculated from 120 technical grade BASF Fipronil samples. These data show that even with the adverse effects of the high halogen content, the data are still sufficiently consistent to differentiate between technical grade Fipronil from BASF and Fipronil from other sources.

This can be visualized by using PCA. PCA is a tool in multivariate statistics that is used to structure and simplify complex data sets. It is typically used for isotopic fingerprinting.

Figure 2 shows a PCA, generated from the data set of BASF Fipronil and the non-BASF sources, that allows clearly the differentiation of BASF Fipronil from Fipronil from the other sources.

**Fipronil Isolated from End-Use Formulated Products.** Fipronil, as most other active compounds used for crop protection, is typically used in formulated form. The term "formulation" refers to the combination of the active compound with other substances, such as emulsifiers, thickeners, stabilizers, and solvents. All of these compounds generate strong interfering effects on the measurement; therefore, Fipronil has to be isolated from the formulation before measurement. Preparative HPLC coupled to ESI-MS and UV−vis detection at 230 nm proved to be a suitable tool to separate Fipronil from formulation compounds. The purity of the isolated Fipronil was confirmed to 99% (w/w) on average by analytical HPLC, coupled to UV−vis and ESI-MS/MS detectors, versus authentic reference material.

To demonstrate the potential of isotopic fingerprinting for the authenticity control of crop protection products as found in the market, Fipronil was isolated by preparative HPLC from formulated end-use products and was analyzed for the isotope ratios

**Table 5. Isotope Ratios of Fipronil Isolated from Formulated Products**[a]

| product | $\delta^{13}$C mean isotope ratio (‰) | SD (‰) | $\delta^{15}$N mean isotope ratio (‰) | SD (‰) | $\delta^{34}$S mean isotope ratio (‰) | SD (‰) |
|---|---|---|---|---|---|---|
| BASF1 | −32.7 | 0.2 | −8.8 | 0.3 | 3.1 | 0.3 |
| BASF2 | −33.3 | 0.1 | −7.0 | 0.1 | 1.5 | 0.1 |
| BASF3 | −34.3 | 0.1 | −7.3 | 0.1 | 0.9 | 0.2 |
| Gen_Prod1 | −32.6 | 0.2 | −4.9 | 0.3 | 5.4 | 0.3 |
| Gen_Prod2 | −32.4 | 0.1 | −9.4 | 0.1 | −2.2 | 0.2 |
| Gen_Prod3 | −32.6 | 0.1 | −10.7 | 0.1 | −2.8 | 0.1 |
| Gen_Prod4 | −25.2 | 0.1 | −3.2 | 0.1 | −13.1 | 0.2 |

[a] $n = 1$.

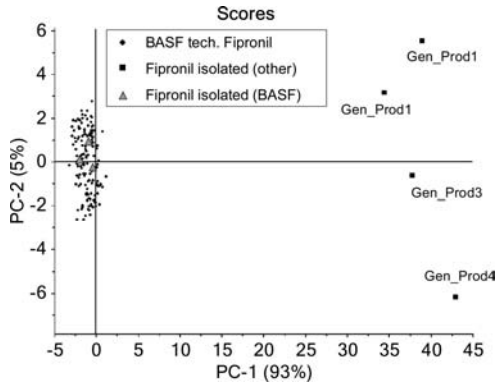


**Figure 3.** PCA of Fipronil isolated from formulated end-use products.

of C, N, and S (Table 5). The preparative isolation of Fipronil did not seem to have an isotopic fractionation effect, or at least only within the measurement tolerances.

Figure 3 shows the PCA of these samples, together with the data set of BASF Fipronil (Figure 3). Fipronil isolated from BASF products aligns well with the data generated with technical grade BASF Fipronil. The non-BASF sources (Gen_Prod1−Gen_Prod4) show a significantly different pattern and are clearly separated from the BASF Fipronil. The differences mainly stem from the $\delta^{15}$N and $\delta^{34}$S values; only one (Gen_Prod4) also differs significantly in the $\delta^{13}$C pattern. One reason for this observation is the use of different building blocks for the synthesis.

This study demonstrates that isotopic fingerprinting is suitable for the analysis and differentiation of crop protection active compounds, both technical grade and active compounds isolated from formulated end-use products. The preparative isolation process did not show a measurable influence on the isotope ratios. Furthermore, the preparative HPLC system used proved to be sufficiently selective enough to remove all interfering formulation compounds.

Whereas in some cases the determination of $\delta^{13}$C and $\delta^{15}$N is sufficient, the measurement of $\delta^{34}$S significantly improves the ability to differentiate between sources. Therefore, a full C/N/S isotope ratio measurement is recommended.

It is understood that compounds with a high halogen content, such as Fipronil, result in high stress for the equipment and, therefore, higher costs of analysis. Fake crop protection products, however, are a hazard to consumers as they may also contain unknown and potentially toxic substances, such as nonregistered byproducts, which are normally not in the focus of analysis. Screening for "general unknowns" in fake products is a highly time-consuming and cost intensive task, as it requires high expertise and the use of dedicated equipment. It is therefore by far more time and cost efficient to confirm the (non)identity of an active compound by isotopic fingerprinting.

## AUTHOR INFORMATION

### Corresponding Author

*Phone: +49 (0)621 6028372. Fax: +49 (0)621 6027162. E-mail: philipp.weller@basf.com.

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