

INTRODUCTION

Many organic contaminants of concern in the environment and food chain are biologically active. This includes residues of pesticides, veterinary medicines and human pharmaceuticals.

Almost by definition, biologically active chemicals are subject to metabolism by animals, plants or microorganisms. Metabolites are formed as a by-product of the biological effect, or as a mechanism for an organism to absorb or excrete the chemical. This mechanism may be obvious in the case of animals or plants, or less so in the case of environmental degradation by the action of microorganisms. Metabolites and degradation products are often much more persistent than the parent chemical. Residues of biologically active chemicals in food or in the environment rarely exist purely as the parent compound.

There will be a range of metabolites and degradation products, which may or may not be of significance. In the case of registered active substances with legal Maximum Residue Levels (MRLs) in food - i.e. pesticides and veterinary medicines - an assessment will have been made if any metabolites are significant in terms of either relative concentration or toxicology, and the MRL will define which metabolites (if any) must be measured and summed. This paper uses a series of examples to illustrate the significance of metabolites in interpreting analytical results, and different approaches to their analytical measurement.



SHOULD ALL METABOLITES BE ANALYSED?

Metabolites are not always significant, and there is often no need to analyse them. But there are a number of reasons, and many examples, as to why it can be important to encompass key metabolites within the analytical measurement.

These include:

- Policing the illegal use of a chemical
- Conducting toxicological exposure monitoring
- Checking compliance with an MRL
- Diagnosing the origin of a residue

Policing illegal use

If a chemical is banned from use, and this is being policed by residue monitoring, then analysis should target the molecule(s) which is unambiguously detectable for the longest period of time after use. In many cases, this will be a metabolite. There is little point in testing for the parent molecule if it would have been metabolised within hours.

Example 1: Nitrofurans

Nitrofurans are a class of antibiotic, used in both veterinary and human medicine. Most veterinary uses were withdrawn in the 1990's, and nitrofurans are now banned from being administered to food-producing animals in most regulatory jurisdictions. For the first few years of the ban no issues were detected, but when test methods were developed for tissue-bound metabolites¹, nitrofurans were found to have still been in use in a number of industry sectors. Nitrofuran parent molecules are completely metabolised within hours in species such as poultry and shellfish. As such, test methods for the parent molecule are irrelevant; residues in meat and fish will only be detected as their metabolites.

Nitrofurans provide a salutary reminder, then, that in detecting a metabolite we can only infer the previous presence of its parent molecule, it does not measure it directly. There may, however, be alternate explanations for a metabolite's presence: repeated detection of semicarbazide, a metabolite of nitrofurazone, was used to justify EU trade restrictions and intensified inspection regimes. But semicarbazide is not solely a nitrofurazone metabolite, and is a relatively small and undistinguished organic molecule. It is now suspected that many of these restrictions were overzealous, with innocent explanations including natural production of semicarbazide from shrimp shell and in cattle stomach lining².



TOXICOLOGICAL EXPOSURE MODELLING

Metabolites, by their nature, tend to be less biologically active than the parent compound. This can mean that they have less potent toxicity. However, there are plenty of exceptions where the metabolite has a higher toxicological potency than the parent. There are also examples where the metabolite has a different toxicological mode of action, which may be of much higherconcern.

Genotoxic and teratogenic metabolites are rare amongst regulatory approved pesticides or veterinary medicines, but there are more frequent examples amongst unapproved products. It is vital to include toxicologically potent metabolites, or those with different toxic effects, in residues tests used to generate data for exposure modelling or risk assessments.

Example 2: Carbadox

The veterinary antibiotic carbadox is, also used as a feed additive to promote weight gain in pigs. Although carbadox itself can have genotoxic and teratogenic effects, in pigs it is completely metabolised. The metabolite, Quinoxalinecarboxylic acid (QCA), is safe. In 1990, the WHO/UN Joint Evaluation Committee for Food Additives (JECFA) concluded that there were no residue concerns from carbadox use in pigs³. On this basis, carbadox continues to be used in the US (it was banned in some jurisdictions, including Canada and the EU, on operator safety grounds and under the generic ban on growth promoters.)

Two intermediate metabolites, desoxycarbadox and hydrazine, had been considered too short-lived to

be relevant. However, modern test methods utilising more sensitive detection techniques demonstrated that trace levels of desoxycarbadox outlasted QCA in edible pig tissues. Desoxycarbadox was suspected as being a more potent mutagen than even the carbadox parent. JECFA therefore revised its opinion stance in 2003, concluding that there was insufficient evidence to set a safe limit⁴. The US Food and Drug Administration have served notice to ban carbadox if the manufacturer cannot provide more safety evidence. Today, analysts measure different metabolites depending on the purpose of the test in question; QCA, when policing a carbadox ban, or desoxycarbadox when conducting exposure or toxicity studies.



Neonicotinoids

Neonicotinoids are a class of systematic insecticides that have been linked to a decline in the honeybee population, contributing to a 45% loss of commercial honeybees in the UK and 40% in the US since 2006. This class of insecticides are used to control a range of sucking, chewing and soil insects. The toxicity of the metabolites occurring within the neonicotinoid class, vary in terms of their toxicity, ranging

from acetamiprid metabolites, which are not shown to be toxic, to clothianidin, a metabolite of thiamethoxam which is even more toxic than its parent. Most bee studies indicate that the metabolites of neonicotinoids largely contribute to observed toxicity, which cannot be predicted and must therefore be taken on a case by case basis.



ENSURING COMPLIANCE WITH A MAXIMUM RESIDUE LEVEL (MRL) DEFINITION

When testing against an MRL, analysts must always refer to the specific legislation to check which metabolites, if any, must be included. This can be dependent upon the crop, and even upon whether compliance is being assessed for the same

residue against either pesticide or veterinary legislation. It is as important to clarify which metabolites to exclude as to which to include in the analysis.

Example 3: Thiabendazole

Thiabendazole is an example of a residue for which the metabolites to be measured depend upon the food type. Thiabendazole can be used both as a fungicide and as an anthelmintic to treat veterinary parasites; in the case of animal products, the MRL is defined under both

EU veterinary⁵ and pesticide⁶ legislation as the sum of thiabendazole and the 5-hydroxythiabendazole metabolite. In all other food types, the MRL is defined under EU pesticide legislation solely in terms of thiabendazole levels.

Care is needed, particularly, when the MRL is defined as the sum of certain metabolites "expressed as" a common moiety. Some test methods used during the original registration studies were designed to capture all similar metabolites by converting them to a common molecule, which is then measured. The MRL is

defined in terms of the μ g/kg concentration of that molecule in the sample. If using a more modern test method, measuring each metabolite individually, then analysts must ensure comparability with the MRL definition by including a mass-conversion calculation to adjust for the molecular mass of each metabolite.

Glyphosate

Glyphosate is a herbicide used to control broadleaf weeds and grasses, that has been banned or restricted in a growing number of countries due to its negative health and ecological effects. The main metabolite of glyphosate,

a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

(AMPA), has been shown to be just as persistent and toxic as glyphosate itself. Legislation for animal products and certain crops include AMPA in the residue definition of glyphosate, and therefore require that AMPA is also analysed when reporting glyphosate residues.

Example 4: A Mass Conversion Calculation

The MRL of albendazole, an anti-parasitic veterinary drug, is defined⁵ as the sum of albendazole sulphoxide, albendazole sulphone and albendazole 2-aminosulphone, expressed as albendazole. The MRL for sheep liver is 1000 µg/kg.

Analytical results for each of the aforementioned metabolites must be converted relative to the molecular

mass of albendazole before summing to assess compliance with the MRL. For example, the pattern of metabolites below might at first glance seem above the MRL. But upon conversion to the legal definition, rounded to two significant figures, the sample is compliant.

Analyte	Analytical Result µg/kg	Molecular Mass	Mass Conversion	MRL comparison - sum calculation
Albendazole	20	265	not applicable	excluded*
Albendazole sulphoxide	350	281	350 x 265/281	330
Albendazole sulphone	450	297	450 x 265/297	402
Albendazole 2-aminosulphone	200	239	200 x 265/239	222
MRL Sum Definition	nition			

^{*} although the legislative assumption was that albendazole parent was negligible rather than actively excluded, it is technically excluded from the legal definition

Ensuring that the analytical result is expressed in a way that is comparable to the MRL definition can be difficult. There are even some cases where the metabolite is an active pesticide or veterinary medicine in its own right, and has its own MRL.

For example, carbofuran is the main metabolite of carbosulphan; both are independently manufactured and registered as pesticides.



DIAGNOSING THE ORIGIN OF A RESIDUE

The pattern of metabolites can often give useful diagnosis of the likely source of a residue, to help inform investigations and follow-up action.

This is particularly useful in situations whereit is important to distinguish between legal and illegal use of a substance, or how long ago it was used.

Example 5: Pirimicarb

Pirimicarb is an insecticide used to control aphids in vegetables. It acts both on-contact and systemically, and systemic uptake leads to metabolism. The MRL in salad is defined⁶ only as the parent compound, but metabolites are likely to include N-formyl pirimicarb and desmethyl pirimicarb.

Analysts testing compliance with the MRL would only measure pirimicarb, but analysts testing for illegal use will

also measure the metabolites. For instance, when testing "organic" labelled vegetables, pesticide residue might be found, with no record of it being used in the field. A common defence might be that the pesticide appeared as a result of cross-contamination; e.g. from storage boxes that had been previously treated with the chemical as a biocide. Detection of the metabolites, however, would disprove this hypothesis, as they would infer that the chemical had been applied pre-harvest to the crop.



Example 6: DDT

Residues of DDT are extremely environmentally persistent. Although its use has been banned in most countries for over 30 years, residues from historic DDT use are frequently found in the food chain today.

There are two principal metabolites of DDT: DDE, formed by oxidative metabolism, and DDD, formed by reductive metabolism (synonym TDE.) They are formed both in animals and by micro-organisms, for example in the soil. Over time, most DDT converts to these metabolites.

Technical grade DDT is a mix of mainly two isomers; pp'-DDT and op'-DDT, in an approximate 4-to-1 ratio. Each isomer converts to its respective pp'- or op'-metabolite.

Typical analysis of DDT residues in food therefore entails measuring six analytes: pp'-DDT, op'-DDT, pp'-DDE, op'-DDE, pp'-DDD and op'-DDD.

Historical residues would be expected to be present primarily as DDE, with DDD also present in fish. The pp'-to op'- ratio of each metabolite should be 4-to-1. Any atypical pattern, then, such as a significant proportion of parent DDT, is indicative of recent use or fresh contamination from illegally dumped stocks.

The MRL for DDT is defined⁷ as the sum of four of these six moieties: pp'-DDT, op'-DDT, pp'-DDE and pp'-DDD. When testing compliance with the MRL, only these four substances are measured.

ANALYTICAL APPROACHES FOR MEASURING METABOLITES

There are alternate approaches to the inclusion of metabolites in an analytical measurement:

- Treat each metabolite as an individual analyte
- Screen against a marker residue
- Metabolomics

- Convert of all metabolites to a common moiety
- Biochemical measurement of a common functional group

Treat each metabolite as an individual analyte

This is the simplest approach in concept, and fits in well with modern multi-residue test methods such as GC-MS and LC-MS. Each metabolite of interest is quantified against an individual reference standard. It works less well for secondary metabolites in animals, which tend to be chemically very different from other multi-residues

(secondary metabolites, in this context, are generally formed to clear a chemical from the animal's system: they are often protein-bound, or conjugated to highly polar molecules). It works well when analytical interpretation may require subtle differentiation between different metabolites.

Example 7: Boldenone

Boldenone is an anabolic steroid. As well as being of concern in sports anti-doping, it is used as a growth promoter for cattle, but veterinary use is banned in the EU. This is largely policed by the analysis of animal urine. Boldenone was previously believed to be unambiguously synthetic, but is now known to occur naturally in cattle and sheep⁸. Interpreting whether residues are natural ("endogenous") or synthetic ("exogenous") is not straightforward. Endogenous boldenone occurs in the gut, so faecal contamination in urine samples can give false positive results.

However, such contamination is predominantly signified by the epiboldenone metabolite, whilst synthetic boldenone excreted in urine contains both boldenone and epiboldenone. Boldenone analysis and interpretation depends on the species, sex and breed in question. Urine also contains secondary metabolites, such as the glucuronides of boldenone and epiboldenone. Boldenone and epiboldenone are individually measured; rather than test directly for the secondary metabolites, it is usual practice to repeat the analysis both with and without glucuronide-cleaving conditions, and calculate by difference the presence of glucuronidated metabolites.

When measuring metabolites individually it is important to guard against their interconversion during the test method.

This can be a significant risk; metabolites are, by definition, reaction products of each other.

Example 8: Chlortetracycline

Chlortetracycline is an antibiotic used widely in veterinary medicine. The MRL is defined as the sum of chlortetracycline and its 4-epichlortetracycline metabolite; and these are the two analytes are measured for residue surveillance testing. There are other minor metabolites, depending upon the species, which are not included in the MRL definition and are generally not tested. These include keto-tautomers of both the parent and the 4-epimer.

In the 1990s most analytical methods were based on HPLC with UV or fluorescence detection. In the early 2000s, many laboratories upgraded the detection to LC-MSMS whilst retaining the same extraction and clean-up methods. Validation studies seemed to show comparability. But some laboratories noticed a bias in Proficiency Testing results when using LC-MSMS. Detailed investigations⁹ revealed that, under some conditions, interconversion to the (undetected) keto-tautomers could occur within the MS source.

SCREEN AGAINST A MARKER RESIDUE

Each additional analyte in a multi-residue measurement adds to the cost, entailing additional calibration, spiking recovery calculation and validation studies. For a multi-residue method for 400+ pesticides it would be impractical to also calibrate against all relevant metabolites.

It is usual in such cases to choose the molecule likely to be present at highest concentration – either the parent or a metabolite – as a marker residue. Only if this is detected is the analysis repeated, for the pesticide of interest with all of the relevant metabolites, rather than the whole multi-residue suite.

Example 9: Phorate

Phorate is an organophosphorous insecticide. Metabolism is by oxidation, first to its sulphoxide then its sulphone, each of which has an equivalent oxon analogue. Oxidation from the sulphoxide to the sulphone is relatively quick, although the sulphoxide can persist in surface water. The MRL in food is therefore defined¹⁰ as the sum of phorate, phorate sulphone, phorate oxon, and phorate oxon sulphone. Depending upon the crop and the time interval from application, phorate sulphone typically accounts for over half of the total residues.

Many laboratories therefore use this as a marker residue. They assess results against a validated in-house trigger for confirmatory re-analysis seeking all four substances. Typically, this trigger concentration is set at ½ MRL, e.g. 0.0025 mg/kg for those crops which have a phorate MRL of 0.01. The vast majority of phorate sulphone results would be expected to fall below this trigger, and would be reported as negative.



METABOLOMICS

Metabolomics refers to any statistical interpretation of a fingerprint of metabolites. The result is inferred from the overall pattern after comparison with a reference database rather than any individual concentration or ratio. Applications in residues testing include testing for growth promoter abuse in veterinary medicine and for sports anti-doping testing.

Accurate quantification of each metabolite can be vital, and so this approach needs large numbers of esoteric reference standards and isotopic internal standards. Reference databases must be fully representative of the test sample: for example the same cattle breed or feeding regime. They are expensive to construct and maintain. For this reason, metabolomics tends to be reserved for use investigating high-profile suspicious results, research work, or testing elite athletes or racehorses.



Example 10: Testosterone

Testosterone is a growth promoter important in both sports anti-doping and veterinary residues testing. It is also, however, a natural hormone present in all animals. The enhanced urinary concentration following abuse is insignificant compared to the natural variation, particularly within males. It is therefore difficult to set analytical threshold values, even when looking at ratios within a panel of metabolites and isomers.

Testosterone is an androgen. The metabolic pathway of androgens is extremely complex¹¹, leading to variation

in urine concentrations of a host of metabolites. The statistical pattern of the concentrations of multiple metabolites – maybe 10 or 20 different analytes - can be compared to patterns from a reference database produced from untreated animals or athletes. After multi-component analysis (MCA), results in the reference database can be plotted to be visualised as distinctive clusters. A sample pattern that falls outside of these clusters would be suspicious.

CONVERT ALL METABOLITES TO A COMMON MOIETY

Sometimes there are too many potential metabolites to list, they may not be fully characterised, or it might be impractical to measure them individually. An alternative approach is to design an in-situ derivatisation method to convert all metabolites of a common class to a common molecule, and then measure this single product.

If this was the approach used to generate the residue data submitted as part of the original licencing application, then the MRL will be defined on the assumption that a similar method is used for residues surveillance monitoring.

Example 11: Ceftiofur

Ceftiofur is a cephalosporin antibiotic used in veterinary medicine which converts to a complex range of conjugated desfuroylceftiofur metabolites. All cephalosporins, in common with penicillin antibiotics, all contain a betalactam ring structure, a cyclic arrangement of three carbons and a nitrogen. The ceftiofur Maximum Residue Level (MRL) is defined as the "sum of all residues retaining the betalactam structure expressed as desfuroylceftiofur."

This definition assumes a standard approach to testing. All desfuroylceftiofur conjugates are converted to free desfuroylceftiofur, for example by treatment with dithioerythritol in a borate buffer. Free desfuroylceftiofur is unstable, so is derivatised to desfuroylceftiofur acetamide prior to measurement. This means that a mass-conversion calculation must be applied to all results, to account for the mass difference between the acetamide and desfuroylceftiofur.

BIOCHEMICAL MEASUREMENT OF A COMMON FUNCTIONAL GROUP

Test methods such as immunoassays are selective to functional This can be desirable (if the intent is to detect any metabolites groups rather than specific analytes. As such, they are likely to measure all similar metabolites indiscriminately.

of a class, including any uncharacterised metabolites) or undesirable (if selectivity is desired between the parent and metabolites).

Example 12: Florfenicol

Florfenicol is one of the world's best selling veterinary antibiotics, with a range of uses in different species. Florfenicol amine is the major metabolite in meat and tissue samples. The MRL is defined⁵ as the "sum of florfenicol and its metabolites measured as florfenicol amine". Most laboratories approximate this to the measurement of florfenicol amine plus florfenicol. Florfenicol has no approved use for milking cows, and there have been no published studies on its metabolism in milk. The assumption has been that florfenicol amine would be present to some degree, and monitoring for florfenicol amine and florfenicol residues in milk had shown no evidence of illegal use.

In 2016 a UK immunoassay manufacturer conducted a speculate survey of farm-gate milk using a range of different antibodies. One of these was raised against florfenicol, but also cross-reacted to the amine and could be assumed to cross-react to any similar metabolites. The survey produced some positive results¹², which uncovered the illegal use of florfenicol in dairy cows. Work is still ongoing to determine whether residues in milk are present as florfenicol amine, or as some previously uncharacterised metabolite.

CONCLUSIONS

Metabolite analysis is an integral part of testing for trace organic residues. It is important to understand in detail which metabolites should be included in an assay, which should not, and the best analytical strategy to measure them and interpret the results.

The examples in this paper illustrate that such decisions are not always straightforward and can be dependent upon the residue, the sample type, and the purpose of the analysis.

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ABOUT THE AUTHOR

John Points is a UK-based independent consultant, offering advice to the food industry, regulators and laboratories on contaminant and authenticity testing strategies. He previously headed a laboratory specialising in residues in food and anti-doping analysis. He is a member of the UK Expert Advisory Committee on Pesticide Residues in Food, and is a past member of the Veterinary Residues Committee.

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PRODUCTS AVAILABLE

Below is a list of reference materials that are available from LGC, for the analytical examples provided in this white paper:

	Chemical	Part number	Part description	Unit
Example 1	Semicarbazide	DRE-C16933500	Semicarbazide hydrochloride	100 mg
	Nitrofurazone	DRE-C15571000	Nitrofurazone	250 mg
Example 2	Carbadox	DRE-C10968300	Carbadox	100 mg
	Desoxycarbadox	DRE-C12170150	Desoxycarbadox	10 mg
	Quinoxalinecarboxylic acid (QCA)	DRE-C16713000	2-Quinoxalinecarboxylic acid	100 mg
Example 3	Thiabendazole	DRE-C17450000	Thiabendazole	250 mg
	5-hydroxythiabendazole	DRE-C17450500	Thiabendazole-5-hydroxy	10 mg
Example 4	Albendazole	DRE-C10065000	Albendazole	100 mg
	Albendazole sulphoxide	DRE-C10065400	Albendazole-sulfoxide	10 mg
	Albendazole sulphone	DRE-C10065300	Albendazole-sulfone	10 mg
	Albendazole 2-aminosulphone	DRE-C10065200	Albendazole-2-aminosulfone	50 mg
	Carbofuran	DRE-C11010000	Carbofuran	250 mg
	Carbosulphan	DRE-C11030000	Carbosulfan	250 mg
Example 5	Pirimicarb	DRE-C16250000	Pirimicarb	250 mg
	N-formyl pirimicarb	DRE-CA16251300	Pirimicarb-desmethyl-formamido	10 mg
	Desmethyl pirimicarb	DRE-CA16251000	Pirimicarb-desmethyl	10 mg
Example 6	DDT	DRE-C12080000	Description on website = DDT (technical)	250 mg
	pp'- DDT	DRE-C12082000	4,4´ - DDT	100 mg
	op'- DDT	DRE-C12081000	2,4´- DDT	50 mg
	pp'- DDE	DRE-C12041000	4,4´ - DDE	100 mg
	op'- DDE	DRE-C12040000	2,4´ - DDE	50 mg
	pp'- DDD	DRE-C12031000	4,4´ - DDD	250 mg
	op'- DDD	DRE-C12030000	2,4´ - DDD	100 mg
Example 7	Boldenone	DRE-C10662000	Boldenone	10 mg
	epiboldenone	TRC-B675105-10MG	117alpha-Boldenone	10 mg
	Boldenone glucuronide	NMIAD862	17-beta-Boldenone glucuronide potassium salt	1 mg
Example 8	Chlortetracycline	DRE-C11509100	Chlorotetracycline hydrochloride	250 mg
	4-epichlortetracycline	DRE-C13175500	4-Epichlortetracycline hydrochloride	5 mg
Example 9	Phorate	DRE-C16080000	Phorate	100 mg
	Phorate sulphone	DRE-C16088000	Phorate-sulfone	100 mg
	Phorate oxon	DRE-C16085000	Phorate-oxon	25 mg
	Phorate oxon sulphone	DRE-C16085500	Phorate-oxon-sulfone	10 mg
Example 10	Testosterone	DRE-C17322500	Testosterone	250 mg
Example 11	Ceftiofur	DRE-C11065000	Ceftiofur	100 mg
	Desfuroylceftiofur	TRC-D289980	Desfuroyl Ceftiofur	2.5 mg
Example 12	Florfenicol	DRE-C13665000	Florfenicol	250 mg
	Florfenicol amine	DRE-C13665020	Florfenicol-amine	10 mg
Additional Examples	Acetamiprid	DRE-C10013000	Acetamiprid	100 mg
	Clothianidin	DRE-C11691700	Clothianidin	100 mg
	Thiamethoxam	DRE-C17453000	Thiamethoxam	100 mg
	Glyphosate	DRE-C14050000	Glyphosate	250 mg
	Aminomethyl phosphonic acid	DRE-C10205000	Aminomethyl phosphonic acid (AMPA)	100 mg



