

## ‘Sniffer dogs’ working for the agrochemical industry

**As a chemistry student in the 1980s, Thomas Class focused on the investigation of environmental toxins such as dioxin and PCB under the supervision of Professor Karlheinz Ballschmiter. Back then, everybody was talking about the “environment”. The public as well as students and professors at the University of Ulm were all fascinated by the subject. Ulm University institutes were renamed to reflect this interest in the environment. While some of the institutes’ names later changed once again, Dr. Class has retained the same interests and has even stayed in the same place, at the “Eselsberg” site, which also houses the University of Ulm campus. However, rather than pursuing an academic career, in 1992 Class decided to establish PTRL Europe GmbH, a contract research company.**

Ulm-based PTRL Europe GmbH works for big agrochemical companies such as BASF, Bayer, Dupont, Dow Chemicals or Sumitomo for whom it analyses fungicides and pesticides. The company’s clients also include smaller companies that sell patent-free plant protectants. The application of plant protectants needs to be approved by public authorities and thorough testing is required before marketing authorisation can be obtained. This process is fairly similar to the process used to apply for marketing authorisation for medicines. Following EU legislation, studies are carried out to assess the compounds’ environmental toxicity and degradation products. Residues of plant protectants must not be present in plants that are fed into the food production processes.

Class does not investigate naturally occurring toxins such as aflatoxins produced by many *Aspergillus* species that can contaminate grain before harvest or during storage. Instead, he is interested in man-made substances that might persist in the environment for a long time without undergoing physical, chemical or biological changes.

Plant protectants inevitably enter the environment and are potentially also contained in food. This is why the approval and application of plant protectants is strictly regulated in Germany; plant protectants have been subject to registration since 1968. Requirements for plant protectants have become more stringent over time. According to information from the German registration authority, the Federal Agency for Consumer Protection and Food Safety, plant protectants are nowadays among the most widely-studied chemical substances.

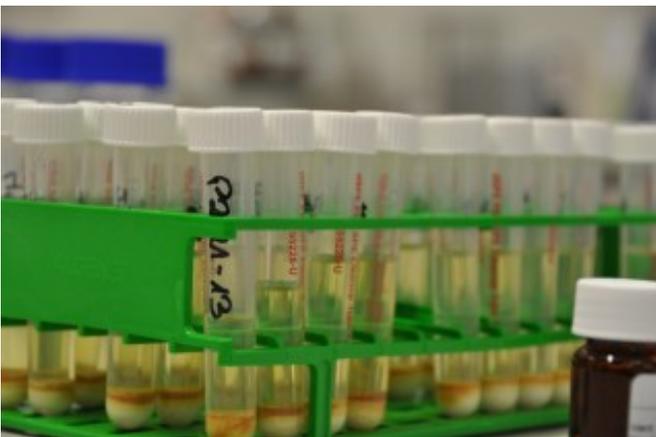


Thomas Class and a food chemist analysing measurement values of a food sample. © Pytlik

## Comprehensive dossier with data and tests

Regulations governing the use of active substances in plant protection products within the European Union are laid down in Directive 91/414/EEC; all active substances used in plant protection products are assessed in a co-decision procedure; the granting of marketing authorisation for a trade product is subject to the decision of the individual EU Member States. A company seeking marketing authorisation for pesticides must present a comprehensive dossier with data sets and tests. The documents must provide information on a product's physical and chemical characteristics, its efficacy, toxicology, potential residues and environmental behaviour. The studies need to be carried out by certified institutions in conformance with valid standards.

## Studies assessing the efficacy of old and new substances



Highly-sensitive analytics are required for assessing the efficacy and toxicity of new pesticides. © Pytlik

PTRL Europe carries out studies on extensively tried and tested plant protectants that need a follow-up registration. Class pointed out that such studies involve highly sophisticated analytical equipment and are not always easy to carry out. PTRL also carries out studies on plant protectants under development that are to be submitted for first-time registration. Class also highlighted that the new pesticides are around a factor of 100 more effective than older ones; in addition, they interfere even more specifically with pest organisms, which reduces the

risk of resistance. These modern substances represent quite a challenge for analytical chemists who have to investigate much lower concentrations of the active ingredients. Some years ago, environmental chemists would not have been able to detect such small concentrations. Nowadays, the substances are manufactured in such a way as to only remain in the environment as long as they are exerting their effect.

PTRL was originally chosen as the acronym for Pharmacological and Toxicological Research Laboratory. Although Class still uses the acronym, he does not hide the fact that it now has very little to do with the company's original activities. Nowadays, PTRL stands for two companies, one of which is located in the Bay Area close to Berkeley and is run by Luiz Ruzo (PTRL West) who co-founded PTRL Europe GmbH with Thomas Class in the Ulm-based Science Park in 1992. The two laboratories - one of them located near the Pacific Ocean and the other near the river Danube - focus on contract research for companies seeking marketing authorisation for pesticides and biocides, as well as chemicals (according to REACH - Registration, Authorisation and Restriction of Chemicals).

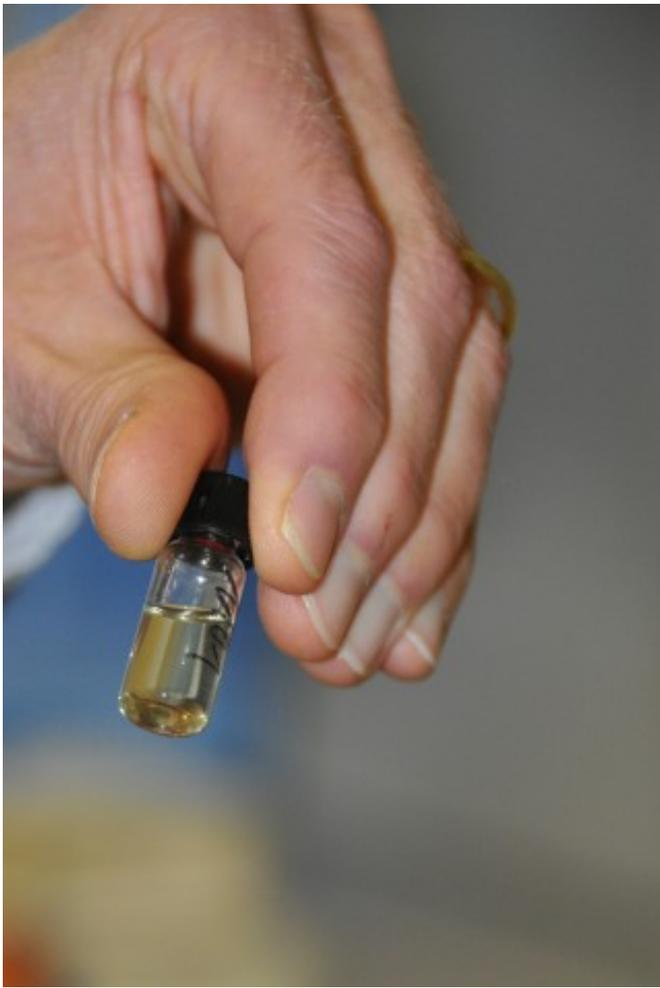
## At the Pacific Ocean and the Danube

PTRL Europe GmbH has thirty employees, two-thirds of whom are academics, chemists, biologists, food chemists and food technologists. In its laboratory in the Ulm-based Science Park I, the company deals with analytical chemistry and theoretical knowledge that has come out of the University of Ulm that can be used for practical applications. Class spent two years as a postdoctoral researcher at the University of Berkeley where he dealt intensively with pesticides. During his time at Berkeley, Class met his American partner who has close links with PTRL Europe GmbH.

The company's laboratories in Ulm deal with the investigation of pesticides in plants, as well as in vegetable and fruit samples. The limit of determination is generally around 0.01 milligram pesticide per kilogram fruit or vegetable. Class explains that food produced with conventional methods often contain pesticide residues, something he does not find surprising as strawberries imported from the southern hemisphere during the winter months need to survive their long journey.

## Looking for pesticide residues in a broad range of samples

PTRL Europe GmbH can identify such chemical compounds, as well as compounds used in baby food where guidelines that are 10 times stricter than those for other foods need to be adhered to. The laboratories are equipped with many instruments, including LC/MS devices that are used to analyse active ingredients and metabolites of pesticides in a broad range of different samples. LC/MS devices, which combine chromatography systems with mass spectrometers, are used to separate compounds from one another, identify and/or quantify them. The sample material that is analysed for the presence of pesticide residues comes from a broad range of areas, including agricultural harvests, soil, ground-, drinking- and surface water, as well as animal products such as milk, egg or meat. The meat of cows fed with corn silage might potentially contain (harmless) pesticide residues. The PTRL researchers are tasked with showing how a cow metabolises such substances. In order to carry out their work, they are constantly developing and validating analytical methods.



Samples of Spanish peaches – what kind of residues can be found in these? © Pytlik

The PTRL laboratories also use gas-phase chromatographs in combination with mass spectrometers, a technology that was used to analyse environmental toxins in the 1980s and 1990s, as Class recalls. The Ulm-based contract research institute also uses radioactively labelled substances that are specifically suited for investigating the metabolism in soil, plants and animals. Radioactively labelled tracers are used to monitor the metabolism of the substances on the molecular level. The company's radioactivity laboratory is equipped with systems for measuring radioactivity, such as liquid scintillation counters, devices that enable the measurement of the energy and intensity of ionising radiation.

PTRL Europe GmbH is currently working for a big chemical company that is planning to renew the marketing authorisation of a fungicide that has been on the market for many decades. It is worth noting that marketing authorisation for pesticides lasts a maximum of ten years before it needs to be renewed. The renewal requires companies to carry out studies according to EU regulations before marketing authorisation is granted, including investigations assessing the degradation of the substance under investigation in the soil, or its behaviour in the environment.

## Are animals and earthworms not affected?

The design of studies that need to be carried before marketing authorisation can be obtained for a specific pesticide has become more and more detailed, requiring companies to take into

account state-of-the-art scientific knowledge. New requirements include, for example, investigations on potential damage to useful animals such as bees and earthworms. When a company contracts PTRL, PTRL will synthesise a fungicide, for example, and label it with radioactive C-14 atoms in order to monitor the degradation products in soil and water. If the fungicide does not dissolve in water and is slightly volatile, the fungicides then require sophisticated analyses and the particular expertise of the PTRL researchers. In such cases, the other degradation products will be analysed and aqueous photolysis will be tested to see whether it is different from normal and whether other chemical compounds are bound to the degradation products. Subsequently, the substance under investigation will be applied to moist or active soil samples and illuminated.

The radioactive substance is subsequently applied to living soil in the dark, the soil samples are incubated and the duration of microbial degradation and resulting products determined. If toxic compounds are detected, further analyses will be carried out to find out how long it takes before the toxin is completely mineralised, whether it is incorporated into the soil or released as radioactive carbon dioxide. Another study will be undertaken to investigate how the substance is metabolised under anaerobic conditions because fungicides can also be found in oxygen-free soil sediments. The researchers from Ulm are interested in finding out whether the substance is degraded more slowly under oxygen-deficient conditions and whether other metabolites are generated.

## No administrative tasks leaves time for essential things

All studies undertaken with the purpose of obtaining marketing authorisation for a pesticide need to conform to good laboratory practice as stipulated in the German Chemical Law. The law also requires the laboratory to undergo certification procedures at four-year intervals. PTRL not only prepares study packages, but also deals with individual studies. "We are a small but powerful organisation," said Thomas Class highlighting the advantages of his company that exists without administrative superstructure. This enables the company to thoroughly plan studies and carry them out quickly, said Class who is both scientific as well as financial director of the company and so is able to approve the purchase of technical equipment himself without going through several bureaucratic layers.

The Ulm-based company is thus able to work on around twenty studies simultaneously. It takes the company between one and three months to prepare a study, including the preparation of a sixty-page report that needs to be written in English. More complex long-term studies can take one to three years, for example the identification of metabolites arising from a pesticide developed by the Swiss company Syngenta.

"Quality can only be proven over time," said Class. Studies have a long-term effect and also provide the basis for decisions as to whether the contracting company can continue the production of a fungicide or herbicide or not. In the 20 years or so since its establishment, the Ulm-based company has made a name for itself in the agrochemical sector. Class draws attention to the fact that PTRL does not need to promote its services with glossy and expensive advertisements, so freeing up the company for its direct business activities.



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## Article

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## The article is part of the following dossiers



Environmental toxins: effect and origin