charles river

SAFETY ASSESSMENT

Agrochemical Development Services

Conducting agrochemical regulatory testing for over 40 years

Achieving development milestones is highly dependent on good communication, minimizing technical deviations, and satisfying regulatory expectations. Having a development partner with an integrated network of experienced scientific staff who have been troubleshooting unexpected toxicity or other issues as a team for many years will greatly benefit a product's development timeline.

The key to quick communication and resolution of any issues that arise comes down to how easily the scientific and technical experience of a program is shared between the different teams. Staying one step ahead of the constantly changing regulatory landscape makes it easier to dedicate the appropriate resources and ensure compliance.

Charles River has been serving the testing and regulatory needs of the world's agrochemical companies for nearly half a century, collaborating in the development and registration of new and existing active ingredients and formulations. With particular expertise in the design of tailored study programs to meet the regulatory needs of new products and their intended markets, we have a very flexible approach to partnership with our customers. We offer a comprehensive service to manage the development of agrochemicals and are experienced in the conduct of full safety evaluation programs. We have comprehensive laboratory and animal facilities offering a wide range of required studies including chemistry, toxicology, metabolism, environmental studies, field trials, residue analysis and human exposure studies. As an established, full service contract research organization, Charles River services also include specialist regulatory consultancy to fully support the conduct of agrochemical development programs.

Services:

- Product and Analytical Chemistry
- ADME
- Toxicology
- Human Exposure Studies
- Residue Studies
- Environmental Sciences
- Regulatory Support

EVERY STEP OF THE WAY

Product and Analytical Chemistry

5-batch Analysis

Our chemists have expertise in the separation, identification, synthesis and quantification of impurities that may be present as a very small proportion of structurally similar or isomeric materials. We can develop a rational and cost-effective program for identifying and quantifying these impurities within production batches to obtain the minimum regulatory closure of 98% w/w required for approval.

Physicochemical and Stability Testing

Charles River offers a range of physicochemical tests for both active ingredient and formulated product. Studies are performed according to the appropriate OECD, OJEU, CIPAC and/or OPPTS guidelines. We can determine the storage stability and shelf life of formulated products under a variety of storage conditions. Facilities are available to stress materials using monitored heat, humidity or light parameters.

Analytical Capabilities

Analysts are available to establish analytical methods or develop existing methodology using a wide range of up-to-date equipment. A suitable, validated analytical method is required to support many required product chemistry and ecotoxicology tests. Before a toxicity study begins, appropriate formulation and analytical methodologies are developed and validated. This allows us to verify accuracy and homogeneity and establish stability data for dose formulations.

ADME

Charles River offers a complete range of metabolism studies in support of agrochemical development and has extensive experience in conducting studies designed to investigate ADME properties of active substances in laboratory animal species and in human and animal tissues/cells *in vitro*. Our experienced scientists routinely conduct mass balance and tissue distribution studies to determine tissue half-life, clearance rates and potential sites of toxicity after systemic exposure. Protocols are developed with clients to satisfy appropriate regulatory requirements.

Toxicology

We design and perform integrated (*in silico, in chemico, in vitro* and *in vivo*) safety programs to best characterize potential human toxicity. Our staff of toxicologists, pathologists, veterinary surgeons, regulatory specialists and support personnel possess a strong mechanistic understanding of toxicity, bolstering our ability to determine potential risk factors throughout the development process.

Genetic Toxicology

Genetic toxicology studies are conducted early in safety evaluation programs for new agrochemicals to assess potential for induction of genetic mutations or chromosomal damage. We offer a comprehensive range of *in vitro* and *in vivo* genotoxicity assays that can be integrated into a standard toxicology program to predict potential long term adverse health effects.

In Vivo Irritation and Sensitization Studies

We provide a range of *in vivo* dermal and ocular irritation and sensitization studies should these still be a necessary component of a particular program.

Acute Toxicology

We offer acute toxicology testing to define intrinsic toxicity of a test item and provide data for establishing risk assessment of acute exposure to a test item. Information generated in acute studies is useful in design and selection of dose levels for repeat-dose toxicity studies.

Ocular Irritation

In compliance with the 3Rs, we offer alternative *in vitro* testing for several applications. The BCOP (OECD Test Guideline No. 437) and EpiOcular™ (OECD Test Guideline No. 492) can be used in a top-down and bottom-up testing strategy to give classifications for ocular irritation and serious eye damage. The *in vivo* animal testing method (OECD Test Guideline No. 405) may finally be used where there is an established regulatory testing requirement or that a complete classification has been achieved *in vitro*.

Skin Irritation and Corrosion

A similar approach is taken in the skin. *In silico* (e.g. Derek, Nexus) screening can be used to initiate the testing programme, and *in vitro* 3D reconstructed human skin models (e.g., EpiSkin® or EpiDerm) are used to classify dermal corrosion (OECD Test Guideline No. 431) and irritation (OECD Test Guideline No. 439). Both models may be used directly to replace animals, subject to regulatory requirements and acceptance. The *in vivo* animal testing method (OECD Test Guideline No. 404) may finally be used where there is an established regulatory testing requirement or that a complete classification has been achieved *in vitro*.

Skin Sensitization

Skin sensitization testing utilizes *in silico, in chemico, in vitro* and *in vivo* tests in a stepwise testing strategy. This starts with *in silico* (DEREK), then progresses through the *in silico* assay, DPRA (OECD Test Guideline No. 442C), through to the *in vitro assays*, h-CLAT (OECD Test Guideline No. 442E), U-SENS (draft OECD Test Guideline), and/or KeratinoSens (OECD Test Guideline No. 442D) and finally through a weight of evidence evaluation which may utilize read-across or unvalidated methods. Where there is an established regulatory testing requirement or that a complete classification has been achieved *in vitro*, *in vivo* tests may then be performed. Usually, in Europe this is the LLNA (OECD Test Guideline No. 429) and in US this is the Buehler test (OECD Test Guideline No. 406).

Repeat-Dose Mammalian Toxicology

Our portfolio includes a range of repeat-dose toxicity studies using regulatory-acceptable rodent and nonrodent species. Studies are designed to detect physiological, biochemical, hematological, immunological, neurological and pathological effects of a test item. Studies range from dose range finding to subacute, subchronic and chronic exposure studies.

Developmental and Reproductive Toxicology

We conduct all standard OECD/EPA guideline studies for developmental and multigenerational reproductive toxicity, including Extended One-Generation Reproductive Toxicity Study. Our developmental toxicity experts can also conduct studies that include adult and developmental neurotoxicity and adult and developmental immunotoxicity, as well as endocrine disruptor evaluations.

Long-term Toxicity and Carcinogenicity

Our study directors and pathologists provide a considerable resource for performing these complex studies, which expose animals to the test item for a major portion of their life span (18-24 months) and assess the development of neoplastic lesions.

Neurotoxicity Screening

Charles River performs detailed functional observations and assessments to satisfy requirements of relevant test guidelines. These are routinely included in all subacute toxicology studies. In-house validation studies in rats using known neurotoxins ensure that techniques used are reproducible and equipment is reliable.

Histopathology and Pathology

Our teams of veterinary pathologists and specialist technicians play a crucial role in the safety assessment of agrochemicals. Qualified and experienced technicians provide necropsy and routine histology services to support our specialist veterinary pathologists in their evaluation of toxicology studies, including reproductive and carcinogenicity.

Skin Absorption

Currently, there are a number of approaches to assess dermal absorption, mainly depending on the regulatory authority to which the data is being submitted. An initial physicochemical assessment providing default values may be all that is required. The two main tests are *in vitro* (OECD Test Guideline 428), Guidance Document No. 28 using human and/or rat skin and *in vivo* (OECD Test Guideline 427). Industry guidance and experience in interpretation of this data is then used to generate the values for the risk assessment. In some cases, a triple pack may be required which is running human and rat *in vitro* and rat *in vivo* either together or in series.

Human Exposure Studies

Exposure studies are performed to evaluate the potential for dermal and inhaled exposure in typical in-life occupational situations (e.g., agricultural operators using knapsack sprayers in the field, glasshouse, home or garden). Our competency in these studies is enhanced by Charles River's unmatched experience with GxP. Using local country offices, we perform both field and residue/analytical portions of operator exposure studies throughout Europe.

Residue Studies

Charles River has an established Residue Chemistry group providing a comprehensive, quality analytical service in support of a wide range of regulatory studies including field residues, soil dissipation and accumulation, animal feeding, environmental toxicology, and aquatic toxicology. We can also perform independent laboratory validations.

Plant Metabolism

Charles River conducts plant metabolism studies with radiolabeled test items in our facilities both in the UK (under glass) and Spain (outdoor). We have grown a variety of species to maturity including legumes, root crops, fruits, salad vegetables, and vines in support of our plant metabolism studies. We also conduct confined crop rotation studies (using radiolabeled test items) and investigations into degradation during storage and processing. Specialist studies include investigations into effects of pesticide treatment on biochemical reactions.

Livestock Metabolism

Charles River has over 25 years of experience with the different types of metabolism and residue studies required for compliance with European, US and Japanese regulations, working with all common livestock species and routes of administration. Our experience in formulating doses is diverse, ranging from aquatic-based solutions to oil-based suspensions. ADME studies are conducted using radiolabeled test items in a variety of livestock species. The majority of our studies are carried out for compliance with the requirements of the US EPA and European regulatory agencies.

Field Trials

Charles River has been conducting full-scale field trials for nearly 20 years, operating in the UK and throughout Europe. We offer a comprehensive range of field trials and associated studies, including residue, efficacy, tolerance, selectivity, and soil dissipation or accumulation studies. All studies can be conducted at designated field offices throughout Europe or through an established network of field trial collaborators within countries situated in northern, central and southern Europe.

Environmental Sciences

Our team of environmental scientists are experienced in conducting the studies required to assess environmental risk of agrochemicals. These experts, together with regulatory affairs consultants, can advise on study programs and individual study designs. We give special attention to the design of single protocols that satisfy the requirements of more than one regulatory authority.

Ecotoxicology

We can perform ecotoxicology studies to determine potential toxicity to aquatic organisms, soil organisms and terrestrial plants. We provide a full analytical service for the method validation and routine analysis required in support of many aquatic studies. We routinely handle difficult test items (e.g., volatile, unstable or partially soluble), and have the facilities and equipment to deal with complex test situations. If necessary, any particular test can be conducted with radiolabeled test items.

Environmental Fate

Charles River offers a range of environmental fate studies, including aerobic and anaerobic degradation in soil, sediments and associated surface waters, soil adsorption/desorption investigations and degradation of agrochemical products in manure, slurry and soil. We can also design bespoke study protocols to address unique situations (e.g., volatility, persistence).

Endocrine Disruptor Screening Program

Charles River offers the complete package of Tier 1 endocrine disruption screening assays as presented in the US EPA Endocrine Disruptor Screening Program (EDSP) as well as the OECD test methods for assessment of chemicals for endocrine disruption. All tests are fully validated and can be performed under GLP or non-GLP screening conditions. In addition, Charles River offers regulatory support and consultancy services.

Regulatory Support

Charles River is experienced in active substance submissions (both chemical and (micro) biological) in Europe and has successfully supported plant protection product authorizations in European Member States. Our in-house expertise covers all areas and we can prepare study waivers and high quality study summaries, develop testing strategies, perform both occupational and environmental (higher tier) exposure model calculations and risk assessments, participate in task forces and produce (CADDY) dossiers for submission to regulatory authorities. These services can be provided either on a project-by-project basis or for the full management of a submission through to final approval.