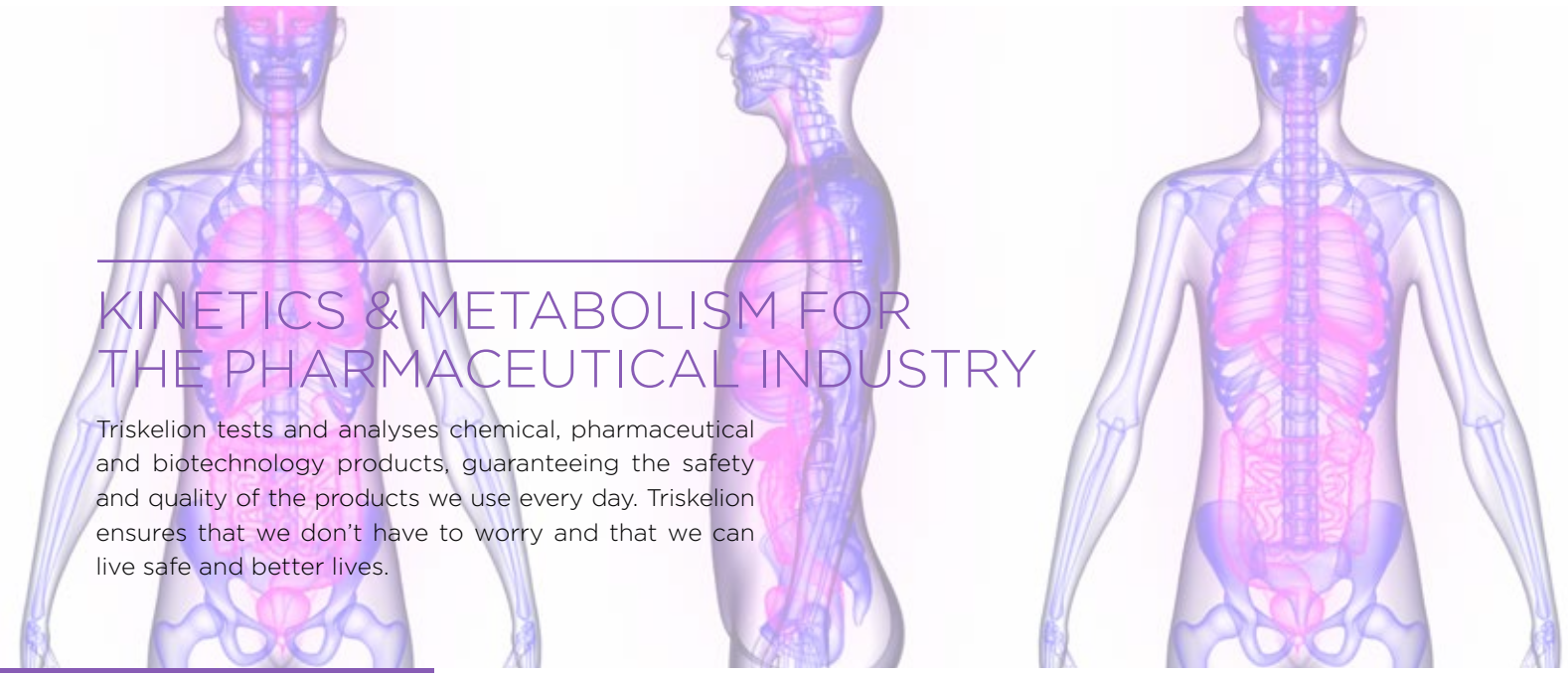
TRISKELION
RESEARCH FOR BETTER LIVING



KINETICS & METABOLISM FOR THE PHARMACEUTICAL INDUSTRY

Triskelion tests and analyses chemical, pharmaceutical and biotechnology products, guaranteeing the safety and quality of the products we use every day. Triskelion ensures that we don't have to worry and that we can live safe and better lives.

PHARMA

CAPABILITIES IN KINETICS & METABOLISM STUDIES:

IN ORDER TO COMMUNICATE YOUR PRODUCT INFORMATION RESPONSIBLY TO THE USER YOU NEED TO HAVE AN UNDERSTANDING OF THE METABOLIC FATE AND BEHAVIOR OF YOUR PRODUCT. TRISKELION HAS OVER 30 YEARS OF EXPERIENCE IN *IN VITRO* AND *IN VIVO* KINETICS AND METABOLISM STUDIES WITH A WIDE RANGE OF (RADIO-LABELLED) TEST SUBSTANCES VIA ALL RELEVANT EXPOSURE ROUTES THAT ARE REQUIRED TO ASSESS SAFETY AND EFFICACY.

We contribute to the development of safe industrial pharmaceuticals and assist in developing a strategy, as well as collecting toxicokinetic, ADME & mode of action data for a mechanism-based risk assessment/evaluation for the safety of your compound according to the regulatory guidelines.

We offer long-standing experience in testing complex molecules, metals, mixtures, volatiles and gases that may enter the body via the inhalation, dermal and oral routes, and are supported by our excellent bioanalytical facilities. Mechanistic studies (mode of action) in combi- nation with our PbPk modeling services will help you to perform a more realistic mechanism-based risk assessment.

TOXICOKINETIC STUDIES

Triskelion offers toxicokinetic studies for various pharmaceuticals under GLP standards, both as stand-alone studies and as part of an integrated safety package with other disciplines, like inhalation toxicology, reprotoxicity (placental transfer), general toxicology, genetic toxicology and immuno toxicology to establish the relationship between the kinetics and the effects of pharmaceuticals. Various dose regimens and all exposure routes can be applied. Toxicokinetic parameters are assessed using the WinNonLin® software program for (non-) compartmental modeling. In collaboration with our partner TNO, Physiological Based Kinetic modeling services are available, all geared to understanding in detail the fate of your compound and its metabolites in the body, including scenario testing, species comparison and route-to-route extrapolation. Plasma protein binding, tissue binding, partition coefficients and metabolic rates can be determined and frequently used as input parameters for PBK models.

COMPARATIVE METABOLISM

To establish differences in metabolic profiles across species various *in vitro* metabolism studies are provided, such as microsomes and cytosol (of various organs) and hepatocytes of all relevant species. Metabolite profiling and identification can be performed using HPLC with on-line radiochemical detection or any other relevant analytical method, like mass spectrometry.
In addition to phase I enzymes, the role of phase II enzymes (glucuronyltrans

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QUALITY ASSURANCE
STUDY ACTIVITIES PERFORMED BY TRISKELION ARE CONDUCTED ACCORDING TO THE PRINCIPLES OF GOOD LABORATORY PRACTICE.

ferases, sulfotransferases, glutathione S-transferases) in metabolism may also be investigated. We have a long track record with these enzymes and can set up assays for specific biotransformation enzymes on request.

ADME & BIOAVAILABILITY & METABOLISM

ADME/mass balance studies are designed to investigate the absorption, distribution, metabolism, and excretion (ADME) of compounds to support safety evaluation in relevant species, including surgical models like bile catheterization. Thirty years of experience provide you with in-depth advice on the most appropriate study design, data collection and interpretation. We have experience with a wide range of radio-labelled test substances (^{3}H, ^{14}C, ^{33}P, ^{35}S and ^{125}I) and arrange custom radio synthesis. Metabolic pathways are established using metabolite profiling and structural identification of metabolites. Tissue disposition assessment and placental transfer can be performed using the classical Quantitative Tissue Distribution technique or (quantitative) whole-body autoradiography (phosphor-imaging) and micro-autoradiography (to assess the disposition compounds at the cellular level).

DERMAL

Full services are provided with respect to both *in vitro* and *in vivo* dermal absorption testing of pharmaceuticals. All studies are performed according to international guidelines. In addition, *in vitro* absorption studies can also be adequately used for cosmetics products. We have experience with various formulations, including gels, creams and small patches. The following *in vitro* systems are available for the study of dermal drug delivery:

1) Different types of diffusion cells (static and flow through)
2) Experience with use of human skin (full thickness, split thickness or epidermal membranes)
3) Use of viable human skin to study cutaneous metabolism. If a radio label is not available, our bio-analytical department is fully equipped to apply other appropriate analytical methods (e.g. HPLC-UV or LC-MS/MS).

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