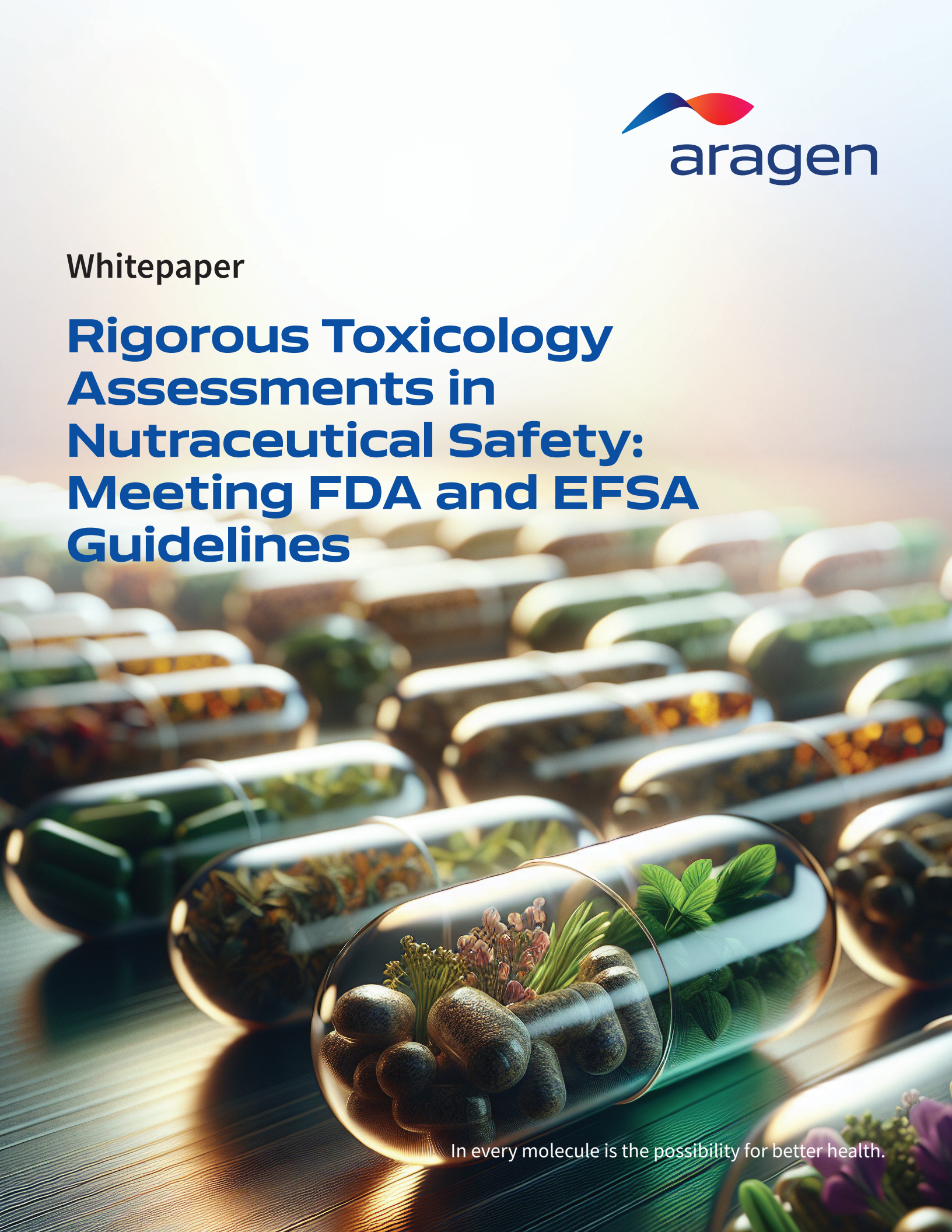
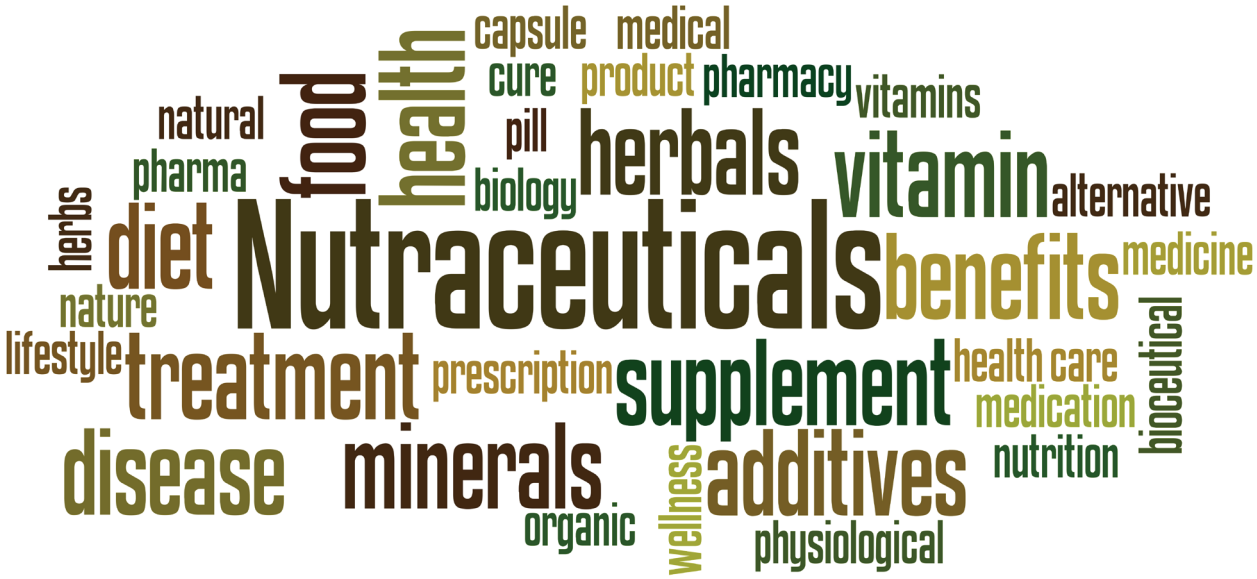
aragen

Whitepaper

Rigorous Toxicology Assessments in Nutraceutical Safety: Meeting FDA and EFSA Guidelines





Executive Summary

As the global nutraceutical industry grows rapidly, regulatory scrutiny by agencies such as the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) is rising to protect consumers and ensure market integrity. Developers of dietary supplements, functional foods, and botanical ingredients must conduct evidence-based, transparent, and well-documented toxicology assessments to meet FDA and EFSA expectations.

Furthermore, the integration of computational toxicology, in silico modeling, and high-throughput screening technologies is transforming safety evaluations. These tools not only reduce reliance on animal testing but also offer predictive insights into ingredient behavior, enhancing regulatory confidence and ethical standards. The convergence of toxicology with data science and artificial intelligence (AI) is also expected to streamline risk assessments and regulatory submissions.

This whitepaper details how modern toxicology—moving beyond reliance on animal models—employs New Approach Methodologies (NAMs) and harmonized global strategies to enable market access, build consumer trust, and accelerate innovation.

Why Toxicology Matters More Than Ever in Nutraceuticals

Nutraceuticals today encompass an ever-growing variety of ingredients including plant extracts, bioactive peptides, fermented products, and novel micronutrients. Many of these are new to the market and lack a substantial history of safe human use, meaning toxicology data becomes a critical aspect of their regulatory dossiers.

In the U.S., ingredients classified as New Dietary Ingredients (NDIs) must be notified to the FDA prior to marketing. This requires:

- **New Dietary Ingredient (NDI) Notifications:** Submission must provide evidence of safety; frequently necessitating toxicology studies tailored to the intended use and population.
- **Generally Recognized As Safe (GRAS) Determinations:** Safety must be demonstrated through either scientific procedures or a well-established history of safe consumption.
- **Adverse Event Reporting:** Mandatory post-market surveillance to identify and manage potential safety signals, ensuring ongoing consumer protection.

In the European Union, the Novel Food Regulation (EU 2015/2283) governs many new nutraceutical components mandating:

- **Comprehensive Toxicological Testing:** Genotoxicity, sub-chronic toxicity, reproductive and developmental toxicity studies.
- **Exposure and Metabolism Assessments:** Analysis of anticipated intake levels, absorption, distribution, metabolism, and excretion (ADME) profiles to inform risk characterization.
- **Qualified Presumption of Safety (QPS):** A streamlined safety assessment applicable to certain microorganisms used in production, reducing data requirements if criteria are met.
- **Scientific Opinions:** EFSA's conclusions derive from peer-reviewed data and thorough risk assessments, forming the basis for regulatory decisions.

For both regions, the quality, relevance, and scientific rigor of toxicology data are critical factors influencing regulatory approval, commercial success, and liability mitigation.

Understanding Regulatory Toxicology Testing Expectations

Meeting FDA and EFSA safety expectations requires targeted toxicological data demonstrating that nutraceutical ingredients are safe under realistic use conditions. Below are the core toxicology endpoints, their purpose, and the specific regulatory requirements in both the U.S. and EU (Table 1).

Table 1: FDA vs EFSA regulatory requirements for safety assessment of nutraceutical ingredients.

Endpoint	Purpose in Toxicology Assessment	FDA Requirement	EFSA Requirement
Genotoxicity	Detects potential DNA damage and mutation risk	AMES test and micronucleus test required	AMES and *in vitro* micronucleus tests are initial screens; if positive, follow up with *in vivo* micronucleus, comet assay, or transgenic rodent mutation assay
Sub-chronic Toxicity	Identifies target organ/systemic toxicity; establishes safe intake levels after repeated exposure (28 or 90 days).	28- or 90-day animal studies, duration based on exposure	Mandatory 90-day studies in rodents for most novel foods
ADME Studies	Determines Absorption, Distribution, Metabolism, and Excretion (ADME), crucial for understanding systemic exposure and accumulation	Case-by-case, not always required	Strongly encouraged for novel foods and new ingredients
Reproductive Toxicity	Evaluates risk to fertility, pregnancy, and offspring development—critical when wide population exposure is possible	Required for broad exposure or sensitive populations	Required when ingredients may be consumed by general/sensitive population
Carcinogenicity	Assesses risk of cancer after long-term or lifetime exposure; informs safe use and labeling	Required based on structural or exposure-based concern	Required for ingredients intended for long-term exposure

A well-designed toxicology program addresses these core endpoints as dictated by regulatory agencies. Satisfying both FDA and EFSA requirements with properly scoped studies and documentation not only enables regulatory approval but also helps build consumer confidence and minimizes post-market risk.

What Makes a Toxicology Assessment Rigorous?

A reliable toxicology assessment is built on traditional methods—hazard identification, risk characterization, and, when appropriate, targeted *in vivo* validation. Besides these, modern assessments like New Approach Methodologies (NAMs) are strategically combined with traditional methods to achieve more human-relevant and efficient safety insights. The use of tiered tests, along with tailored data generation for risk assessment, provides a pragmatic and effective strategy for safety assessment.

Hazard Identification

- **Comprehensive literature review** to identify existing toxicology and exposure data.
- Use of in **silico modeling** to predict hazards based on chemical structure and biological similarity.
- Deployment of ***in vitro* screening** for genotoxicity, cytotoxicity, and oxidative stress markers.

***In Vivo* Validation**

- **Acute toxicity studies** to determine immediate health hazards following a single exposure.
- **Sub-chronic and chronic studies** (typically 28 or 90 days) for identifying cumulative systemic effects.
- **Reproductive and developmental toxicity testing,** important for broad dietary use cases.
- **Carcinogenicity studies** in rare cases where structure or usage indicates potential long-term risk.

Integration of NAMs

- **Human-relevant *in vitro* tools,** including 3D tissue systems, organoids, and organ-on-chip models for target organ toxicity.
- **In silico algorithms** like QSAR or structure activity-based tools (e.g., VEGA QSAR) for predicting genotoxicity and systemic effects.
- **Read-across frameworks** to apply existing data from similar compounds, enabled by shared chemistry and metabolism.
- Use **Threshold of Toxicological Concern (TTC)-derived limits** for risk assessment when toxicity data are limited but exposure is expected to be low, following accepted regulatory guidelines.
- Inclusion of **existing human data** from epidemiological or clinical sources, particularly where post-market surveillance exists.

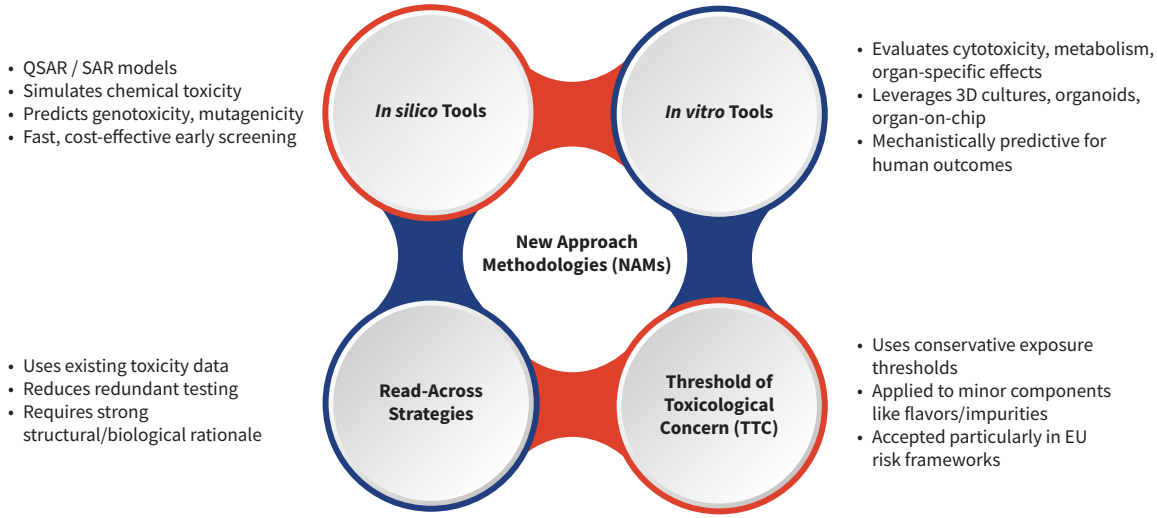


Figure 1: New Approach Methodologies (NAMs) in nutraceutical safety assessment.

Risk Characterization and Dossier Compilation

- Estimate **realistic human exposures** based on proposed dosage form, frequency, and population.
- Define **Margins of Exposure (MOE) and NOAELs/LOAELs** using derived toxicological dose data.
- Compile a comprehensive **regulatory dossier** presenting risk assessments, raw data, method validations, and expert interpretations in formats aligned with U.S. (NDI, GRAS) or EU (Novel Food, EFSA) submission requirements.

Strategic Integration of NAMs in Nutraceutical Toxicology

Regulators around the world are actively encouraging the use of NAMs where scientifically justified, recognizing their value in improving ethical standards while maintaining rigorous safety evaluation. By thoughtfully integrating NAMs with traditional studies, the toxicology program becomes more efficient, ethical, and scientifically powerful. Effective use of NAMs:

- **Improves Relevance:** Provide mechanistic, often human-specific toxicity insights not available from traditional animal models.
- **Increases Efficiency:** Accelerate safety assessments and reduce development timelines.
- **Enhances Ethics:** Reduce animal usage in line with international principles and regulatory momentum.
- **Supports Regulatory Flexibility:** Enable scientifically justified read-across and waivers, reducing duplicative studies and supporting global dossier harmonization.

Additionally, several strategic considerations and emerging tools can further enhance the rigor and regulatory success of toxicology assessments:

- NAMs should be carefully selected based on specific toxicological endpoints—such as genotoxicity, endocrine disruption, or immunotoxicity—and be aligned with regulatory expectations for mechanistic evidence, to maximize their effectiveness. Integrating NAMs with adverse outcome pathways (AOPs) and systems biology improves both interpretability and regulatory acceptance.
- Utilizing global frameworks like ICH and Codex Alimentarius ensures that safety assessments conform to international standards, thereby streamlining regulatory processes and enhancing credibility in emerging markets.

- Digital platforms for regulatory intelligence and submission tracking are increasingly essential. By unifying global requirements, automating documentation, and enabling real-time collaboration, these tools can accelerate regulatory approvals and reduce compliance risks.

Seamless integration of NAMs across all stages of toxicological assessment—from hazard identification through risk characterization—ensures their full potential is realized.

Bridging FDA and EFSA Requirements: A Unified Strategy

While safety is the mutual priority, differences in regulatory philosophies drive distinct submission expectations:

- The **FDA** typically accepts a broad array of data types and formats, with a pragmatic approach that prioritizes safety and feasibility.
- **EFSA** demands strict adherence to internationally recognized standards including OECD test guidelines, GLP compliance, and rigorous documentation.

Given these differences, it is critical to design toxicology programs that satisfy both authorities upfront, facilitating faster global commercialization. To unlock both U.S. and EU markets efficiently:

- **Design studies up front to meet the highest standards** (e.g., GLP, OECD, Redbook) to avoid repetition and increase cross-border dossier acceptance.
- **Capture multiple toxicological endpoints** within individual studies to conserve resources.
- Provide **scientific justifications** for any non-standard approach, especially NAMs or literature-based read-across.

Early consultation with experienced toxicology and regulatory experts is recommended to tailor study design and data packages accordingly.

Conclusion

Innovation in nutraceuticals must be underpinned by rigorous safety evaluation aligned with FDA and EFSA guidelines. By combining classical toxicology with innovative NAMs and adopting a globally harmonized regulatory strategy, companies can accelerate time to market, reduce regulatory risk, and foster consumer trust.

As the regulatory landscape continues to evolve, proactive engagement with authorities, transparent communication of scientific rationale, and continuous investment in safety science will be key to sustaining innovation and public confidence in nutraceuticals.

Companies that embed safety-by-design principles early in product development—integrating toxicology, formulation science, and regulatory foresight—are better positioned to lead in a competitive and compliance-driven market.

About INTOX

Launching new nutraceutical ingredients demands more than innovation—it requires scientific rigor and regulatory precision. **At INTOX**, an **Aragen company**, we specialize in comprehensive toxicology services that align with global regulatory expectations, including **FDA** and **EFSA** standards.

Our expertise covers all stages—from study design and execution to data analysis and regulatory submissions. Whether pursuing GRAS status, NDI notification, or EFSA novel food approval, INTOX ensures your safety data meets the highest scientific and compliance standards. INTOX has successfully conducted multiple studies that have supported regulatory approvals for the various NDI or food additives.

Click here to explore more

www.aragen.com

Aragen is a trusted R&D and manufacturing partner to the global life sciences industry. From concept to commercial, we transform your ideas into solutions for better health. We have more than 20 years of experience providing a range of contract research, development and manufacturing services across the drug development continuum, with a focus on early-stage discovery and development of new molecular entities (NMEs). Whether large pharma or biotech, an agrochemical or animal health company, we provide you global resources and proven capabilities at every stage of the biopharma lifecycle, in small and large molecules. Our ability to offer end-to-end solutions or support standalone programs is underpinned by an innovation mindset, enabling technologies, and a partnership approach to every engagement.
At Aragen, we recognize your work is vital, urgent and impacts lives. Our purpose, 'In every molecule is the possibility for better health' motivates us to drive the success of your programs, so that we can together transform hope into health for millions of people around the world.

Stay Connected