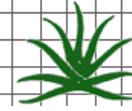


Inside Aloe *Online*



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New Member Benefit



The IASC has entered into an agreement with Grifcon Enterprises endorsing them as the Council's exclusive Products Liability Insurance provider.

See the article below for more details on the endorsement program, contact information, going about getting a quote, and how you can help further support the IASC and possibly save your company money on your premiums for products liability insurance.

Director's Message - Current Events & Status of the IASC



It's been a little more than 3 months since I started as the Executive Director of the IASC, and in that short time we've made substantial progress in a variety of areas beyond the physical moving of the office and operations to the Washington, DC metro area. The Science & Technical committee met and continues to discuss the possibility of an anthraquinone/aloin toxicology study to determine safe levels; the executive

committee approved an endorsement with a product liability insurance provider for the membership that may deliver reduced rates and an additional revenue stream for the Council; the website has been updated and continues to be developed (up-to-date information will be posted regularly on the site, particularly in the "IASC News" section); and the annual science seminar plans continue to be developed.

Most notably is the improvement and continued strength of the certification program. According to members I've spoken with, sales of aloe products continue to be strong, and aloe has been in the news quite a bit of late - from the FDA and its proposed regulations for certain OTC products containing aloe (click [here](#) to see the full story on the IASC website), to the editorial articles such as the one in the IrishTimes - but the most effective method of selling and marketing the quality and purity of aloe and aloe products is the IASC certification program.

It's become obvious to me incredibly quickly how highly valuable it is to have the seal, or being able to have the words "certified by the IASC", on company literature, websites and marketing materials. There's an old saying that I was told when I was a young boy - "anything

worth having is probably worth stealing." I've heard from members several times directing me to the websites and products of companies that are not active participants in the program, but are displaying the seal and/or are using some variant of the words. Understanding that the companies contacting me are paying for the seal and to be part of the program, I can surely understand their concern and want all participants to know that we take misuse of the trademarked materials very seriously.

The program was started to differentiate the upstanding, quality players from the rest - and it is still the goal of the program today. Those of you who are active participants - thank you for your continued support, and the IASC will work to find ways to support you just as you support us - by publishing the list of certified (and non-certified) products and facilities on our website, recommending your products at trade shows and when we receive phone calls, and legal efforts to remove unauthorized certification usage when necessary, for example. While we may not be able to stop every bad player in the industry from displaying the IASC certification program seal, or using language that implies their products are certified, we will continue to address those issues when they arise.

In the coming months the annual science conference will take place and I'll look forward to getting to know many of you personally, and hope you will register and join us for this event. As you'll have no doubt heard, due to the rising costs of travel and other economic stressors, we'll be changing the format of the seminar to be a webinar to be held over a 7-day period in 2-hour sessions. While I will certainly miss the opportunity to meet many of you in person, we hope this shift will allow more people from all over the world to participate as well as save members and company's money and time.

I appreciate all of the support the membership has shown during this transition and look forward to continuing to provide solid leadership, developing new benefits, and bringing greater value and standing to the organization.

A handwritten signature in blue ink, appearing to read "Devon Powell", with a stylized flourish extending to the right.

Devon Powell
Executive Director

New Member Benefit

IASC Enters Into Exclusive Products Liability Insurance Endorsement Program

The IASC Board of Directors recently entered into an agreement with Grifcon Enterprises Inc. to provide members with a comprehensive and competitively priced "Products Liability Insurance Program." Dick Griffin, President of Grifcon Enterprises, Inc. has been providing these services for more than 35 years. He is also currently endorsed by the American Herbal Products Association, the Natural Products Association and the United Natural Products Alliance.



Coverage and pricing are the most competitive available and all insurance carriers are rated "A" or better by A.M. Best. The IASC liability program can be written on the Comprehensive Liability Insurance form which includes Premises Liability, Products & Completed Operations, Premises Medical, Non Owned & Hired Auto, Employers Liability and more, or the program can be written specifically as just "Product Liability" insurance. In either case the Products Liability is written on a "Claims Made" form and provides coverage for "Broad Form Vendors Legal Liability" on a World Wide basis. Primary policy limits are \$1,000,000 Per Occurrence, \$2,000,000 Annual Aggregate and, in most cases, there is a \$5,000 SIR. The program can also provide "Excess Liability" limits up to \$50 million.

All members are eligible to apply for coverage and are encouraged to consider obtaining quotes two (2) months prior to their current policy renewal date. Manufacturers, wholesalers, raw products suppliers and distributors can apply for coverage by asking their current insurance agents/brokers to contact Ms. Denise Pepin, CRC Insurance Services, Inc. (Chicago), Managing General Agents at (312) 899-7332. Insurance agents/brokers will receive 100% of the commission paid. Members, their agents or brokers, who are interested in more information are welcome to contact Dick Griffin at (916) 434-8874.

Annual Science Conference: GENERAL ANNOUNCEMENT



IASC Revamps Science Meeting; New Format Benefits Companies, Environment

The International Aloe Science Council is eliminating airfare, lodging and paper from the 27th Annual Scientific Seminar to reduce its impact on the environment and increase companies' accessibility to cutting-edge research on Aloe vera.

"As the benefits of aloe continue to extend into new product categories and healthcare arenas, the importance of IASC's Scientific Seminar continues to grow," said Executive Director Devon Powell. "There is simply no other opportunity for the scientific community and industry to experience this degree of education and research on Aloe vera."

In light of the broad interest in aloe and the environmental burden of a conventional

conference, IASC is foregoing its traditional in-person meeting in Dallas, Texas. More information on scheduling and speakers will be announced, and interested parties are encouraged to check the IASC website: www.iasc.org.

"With the current slate of speakers, it is clear the research presented at this year's scientific seminar will inform product development for years to come," said Powell. "We are proud to offer it to companies and researchers across the globe in an environmental- and budget-friendly manner."

THE SCIENCE OF ALOE - Recently Published Studies

- [Phytomodulatory potentials of Aloe vera against Salmonella OmpR-mediated inflammation.](#)
- [Investigation of the anti-inflammatory potential of Aloe vera gel \(97.5%\) in the ultraviolet erythema test.](#)
- [\[Determination of trace elements in Aloe barbadensis Miller irrigated with seawater by atomic absorption spectrophotometry\]](#)
- [Effect of Aloe vera whole leaf extract on short chain fatty acids production by Bacteroides fragilis, Bifidobacterium infantis and Eubacterium limosum.](#)

FEATURE ARTICLE



Considerations in Toxicology Study Design and Interpretation: An Overview

By Gradient Corporation: Lewis, AS; Beyer, LA; Langlois, CJ; Yu, CJ; Wait, AD

Introduction

The use of animal data to evaluate the safety of chemicals in humans can be complex. Biological differences among species and the use of high experimental doses often make animal test results difficult to interpret with regard to human relevance. Despite the difficulties, animal studies have formed the cornerstone of toxicology and safety assessments. Animal studies are used to assess a variety of toxicological outcomes: potential noncancer effects, and genotoxicity, carcinogenicity, as well as adverse reproductive and developmental outcomes. Rodents are the most widely used animal models, but other types of animals with special sensitivities may be used for specific endpoints. While it is impossible to eliminate all uncertainty, toxicology studies can be designed to maximize utility and reduce the generation of ambiguous results. Some of the most important considerations of a well-designed study are route of exposure, dose selection, and animal model.

In animal testing, a route of exposure that reflects probable human exposure is key. Without an appropriate route of exposure, study interpretation can be difficult. For example, while it is easier to administer substances to animals using intravenous injection, toxicity information from these experiments may have little relevance to oral exposures. This is because the

toxicity (or detoxification) of a compound may be highly dependent on absorption into the gastrointestinal tract and subsequent metabolism. In addition, oral exposures usually do not reflect dermal toxicity and vice versa.

Dose selection is probably the most complex, but important, decision from a study-design standpoint. One of overall goals of a toxicology study should be to identify a dose associated with no observable adverse effects (called a no-observable adverse effect level [NOAEL]). It is important to establish a NOAEL, which can then be used to establish a threshold of toxicity (i.e., a dose below which no adverse effects are expected). Testing a single dose associated with no adverse effects, however, is often not adequate to determine safety. Because there is some degree of uncertainty between animal and human responses, doses (sometimes well above expected human exposures) should also be tested to demonstrate that there is an ample margin of safety (also called margin of exposure). Many regulatory agencies that register chemicals and products require testing up to doses that are overtly toxic to animals, not only to understand the types of toxic responses that can be expected at higher doses, but also to understand how great the gap (or margin) is between expected human exposures and doses associated with animal toxicity.

What constitutes an adequate margin of safety can be quite complex but, in general, reflects how confident one is that the NOAEL from an animal study will also be nontoxic to humans, even individuals with increased sensitivity (e.g., children, the elderly). As mentioned above, biological differences between humans and test animals are one source of uncertainty. In addition, information about expected human exposures and inter-individual variability in response may also be poorly understood. It should be noted that any safety information based on a history of use in humans will undoubtedly influence perceptions on what constitutes an adequate margin of safety, but at present, there is no formal framework for incorporating this type of information into the design of animal studies. A risk-benefit analysis may also be an important component for certain types of compounds, particularly pharmaceuticals.

Regulatory entities within the US and internationally, often require a prescribed battery of standard studies for product registration. These requirements not only vary across countries, but among different agencies within the same country. The type(s) of proof of safety varies, in part, because the agencies involved in establishing testing guidelines (e.g., Food and Drug Administration [US FDA], Environmental Protection Agency [US EPA], Organization for Economic Co-operation and Development [OECD], etc.) formulate testing regimens for different types of products; examples include industrial chemicals, cosmetics, food additives, dietary supplements, pesticides, and pharmaceuticals. In some cases, there is little or no regulatory guidance. For example, no specific toxicology testing protocol exists for dietary supplements in the US. Even when strict requirements exist, scientific experience is key. Today, regulations recognize the importance of scientific judgment in choosing the type of test, the test species, the duration of the test, and the dose(s) (US FDA, 2007; NRC, 2006). Further, the scientific underpinnings of our understanding of toxicity are continually changing (Hayes, 2008).

Standard Toxicology Tests

Presented below is a broad overview of standard toxicity tests. It must always be remembered, however, that knowledge of the product/ingredient, its structure, and its proposed use should guide decisions regarding toxicity testing. Standard tests by exposure duration are discussed. We have focused on oral exposures. Different tests would be necessary for different exposure routes (e.g., dermal, inhalation).

Acute toxicity: This test, used to evaluate high, short-term exposures, may also help to determine dosing regimens in longer-term tests. If a high dose (e.g., 5,000 mg/kg) is found to

be survivable, no further acute testing is conducted (NRC, 2006). In general, a single dose is given and monitored for several days to weeks after dosing, although compound administration may take place several times within or continuously throughout a 24-hour period. Aside from survivability, acute tests are useful, because they can reveal whether frank toxicity is sudden, delayed, time-limited, or continuous. The time to onset and resolution of toxicity can provide insight into compound attributes such as pharmacokinetics and bioavailability. Importantly, in some cases, previous human experience with a compound may make acute single-dose testing unnecessary (Wu et al., 2008).

Subchronic toxicity: Subchronic studies evaluate the adverse effects of continuous or repeated exposure over a portion of the average life span of experimental animals. Specifically, they provide information on target organ toxicity and are designed to identify NOAELs (NRC, 2006). They can also help determine appropriate dose regimens for longer-term studies. Exposure durations are typically 28 or 90 days. Administration of the chemical is determined by the route of human exposure. Animals are often observed for 2 or 4 weeks after the end of treatment for reversibility, persistence, or delayed occurrence of adverse effects. Typically, doses in subchronic studies are selected to define a dose-response relationship. Toxicological endpoints evaluated include clinical signs (gait, changes in skin, fur, eyes, posture), motor activity, sensory reactivity, body weight, food consumption, and clinical pathology tests (e.g., blood and urine tests). At study termination, gross necropsy is performed and a full histopathological analysis is conducted.

Chronic toxicity: The purpose of a chronic study is to determine cumulative adverse effects of repeated daily oral dermal or inhalation exposures over a 12- to 24-month period (depending on test species). Because of the importance of chronic toxicity, testing is done in two mammalian species (one rodent [rat] and one non-rodent [dog]), as a general rule, though other species can be used with adequate justification. Dose selection is based on the results of subchronic studies. At least three dose groups and a control group should be used. The highest dose should only cause mild signs of toxicity, while the lowest dose should show no adverse effect (NRC, 2006). During the study, body weight and food consumption should be measured along with some clinical pathology tests. At the end of the study, all organ systems are analyzed and a full histopathologic analysis is done (NRC, 2006).

Carcinogenicity: Carcinogenicity bioassays determine cumulative neoplastic effects of repeated exposures over most of the lifetime of the animal. Study design is very similar to a chronic test, and testing is often combined. The carcinogenicity bioassay is conducted with rodents for a minimum of 24 months (rats) and 18 months (mice). Dose selection guidelines are similar to chronic toxicity studies; however, sample sizes are generally larger-50 rodents of each gender per dose group. Further, at the end of the study, extensive gross necropsy and histopathology are conducted to detect neoplasms (NRC, 2006).

Genotoxicity: Genotoxicity testing is performed to ascertain adverse effects on DNA, genes, and chromosomes. It is recognized that many human diseases, and specifically cancer, begin as mutations. Both *in vivo* and *in vitro* genotoxicity tests are available, but *in vitro* tests, which use cell cultures or extracts rather than whole organisms, are relatively quick and much less expensive than animal testing. These tests are designed to detect gene mutations, chromosomal aberrations, and various types of DNA damage.

Although not described here, tests of developmental and reproductive toxicity may also be standard for certain types of chemicals. The results of standard studies may indicate the need for more information on specific endpoints, such as neurotoxicity or immunotoxicity, for example. Also, it should be noted that in many instances, refined follow-up experiments can be useful (but not required) for understanding the biological basis of an adverse effect, which can be helpful when evaluating the relevance of test results to humans (see below).

Study Interpretation

If adverse effects are observed in a toxicology study, the default assumption is that the compound could lead to similar toxic effects in humans. However, in reality, the toxic effects are often not seen in human populations for a variety of reasons including biological differences among species and the fact that high doses (higher than those experienced by humans) are often used in animal experiments. Investigation into potential human relevance can be a complex undertaking requiring a historical perspective on the sensitivity of certain test species to adverse effects, a detailed knowledge of animal and human biology, and an understanding of toxicological interactions on cellular and molecular levels. Several key lines of investigation are mentioned below, but it should be emphasized that evaluating human relevance must be performed on a case-by-case basis—there is no one-size-fits-all approach.

One important consideration is whether the observed effect is a high-dose phenomenon, such that the effect would be unlikely to occur at lower, typical human exposures. This is often the case for noncancer effects, which are expected to operate with a threshold of toxicity. For suspected carcinogens, where it is often assumed that any exposure leads to increased risk, establishing a threshold can be more difficult. However, there has been recent recognition that certain animal tumors occur only when experimental concentrations are high enough to cause tissue damage that leads to a reparative process (Meek et al., 2003).

It may also be important to have a thorough understanding of how the compound is metabolized; the process may be different in animals and humans, resulting in marked differences in toxicity. As an example, theobromine, a compound in chocolate, is fatally toxic to dogs in relatively small doses, because they metabolize theobromine so slowly. Less than 100 grams (or about 3.5 ounces) of unsweetened chocolate can be fatal to a 20-pound dog (Finlay and Guiton, 2005). On the other hand, humans can clearly tolerate and consume chocolate in much higher quantities.

In addition to metabolic differences, humans and animals can also vary biologically in a number of different ways that may modulate responses to chemicals. For example, in rodents, a class of chemicals called peroxisome proliferators binds to a receptor called PPAR- α , which causes abnormal increases in cell proliferation and eventual liver tumors. Although humans have the PPAR- α receptor, they have substantially lower quantities compared to rodents, making humans resistant to PP-induced liver tumors (Klaunig et al., 2003). As another example, rodents are exquisitely sensitive to compounds that disrupt thyroid hormones, while humans have a greater ability to adapt and maintain normal thyroid hormone levels (NRC, 2005; US EPA, 1998).

In conclusion, while testing guidelines are prescriptive for many products, testing for other types of products may be flexible. Regardless, knowledge of the compound, how it will be used, and sound scientific judgment should guide testing decisions. Choosing the appropriate tests and dosing regimens that will demonstrate an adequate margin of exposure is a critical step in establishing human safety. If adverse effects are observed in animal studies, more refined toxicology studies may provide insight on the potential human relevance of observed effects and, depending on the outcome, may offer assurance that effects observed in animals will not occur in humans under intended use scenarios.

*A copy of this article with links to all references may be found on the IASC website or by clicking [HERE](#)

About Gradient Corporation

Gradient Corporation is a nationally recognized environmental and risk science consulting firm with over 20 years of expertise in Toxicology, Risk Assessment, Product Safety,

Contaminant Fate and Transport, and Environmental Chemistry. The company employs sound science to devise and implement cost-effective strategies for addressing chemicals in the environment, in the workplace, and in products throughout their life cycles. From its offices in Cambridge, MA and Seattle, WA, Gradient provides national and international clients with the technical expertise and knowledge required to address their most complex environmental and health related matters. For more information, please visit www.gradientcorp.com

U.S. Regulatory News



FDA's Proposed Rule Anticipated to Have Minimal Impact on Aloe Vera Trade; IASC Solicits Data From Members

The U.S. Food and Drug Administration (FDA) published a notice of proposed rulemaking in the June 19 Federal Register that is relevant to the use of Aloe vera as an active ingredient in two classes of over-the-counter drugs.*

The proposed rule continues a process FDA began in 1972 to address a concern that the agency lacked efficacy data on a significant number of active ingredients being used in OTC drugs. Since 1972, the ingredients identified at the start of the process have been reviewed in batches. For each ingredient under review, FDA asks industry for data to support the use of the substance as an active ingredient in certain types of OTC drugs.* A review of Aloe vera as an active ingredient in topical analgesic drug products and topical antimicrobial drug products was part of a review announced in December 2003. FDA received no data from industry or any other party to support the use of Aloe vera as an active ingredient in these topical drug products. Given the absence of data, FDA published the June 20 proposal that would make the use of Aloe vera as an active ingredient in analgesic and antimicrobial topical OTC drug products unlawful. This proposed rule does not comment on Aloe vera as an inactive ingredient in these two classes of topical OTC drugs.

I have spoken to several Board Members, and we have not been able to identify a product affected by the proposed rule. IASC believes at this time that the impact of this rule on the aloe trade will be insignificant. However, the association would like to hear from any member company if it does supply Aloe vera for use as an active ingredient in an OTC drug product that is regulated under the antimicrobial or analgesic topical monographs.*

Additionally, please keep in mind that this is a proposed rule and is not yet final. If you have excellent efficacy data on the use of Aloe vera as an antimicrobial or analgesic agent, IASC requests you send it to us immediately so the association can prepare a submission to FDA.

Comments on the proposed rule and the economic impact of this proposed rule are due to FDA by Sept. 17, 2008.

*A copy of this article with links to all references may be found on the IASC website or by clicking [HERE](#)

ALOE IN THE NEWS



[South African Flavour Hits New York - Cape Business News](#), August 1, 2008

[State Gives Aloe Vera Farming Job In The Arm - Business Daily Africa](#), August 1, 2008

[Safety & Specifics of Aloe Use - Baltimore Sun](#), July 31, 2008

[The Healing Plant - Baltimore Sun](#), July 31, 2008

[Hair Pioneers Move Onto Natural Alternatives - Exmouth Journal](#), July 23, 2008

[US Farms, Inc. CEO Issues Letter to Shareholders - MarketWatch](#), July 23, 2008

[Soothing Sunburn with Cooling Aloe - IrishTimes](#), July 22, 2008

[Aloe Vera the Healer - From the Gulf Daily News](#), July 13, 2008

[Local Herbs Boost Immune System - The Daily Times](#), July 11, 2008

[Aloe Vera Thriving Despite Lack of Science - Cosmetics Design-Europe.com](#), June 27, 2008

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