Director Sandra Shewry
California Department of Health Services
P.O. Box 997413
Sacramento, CA 95899

October 11, 2004

Re: Response to Letter from International Academy of Life Sciences

Dear Director Shewry,

It has come to our attention that a group known as the International Academy of Life Sciences (IALS), or its subsidiary, PlantPharma, has sent a response to CDFA, Cal-EPA, and CDHS purporting to be supported by the academic community and challenging the validity of our report, "Pharmaceutical Rice in California: Potential Risks to Consumers, the Environment, and the California Rice Industry." The authors slander our groups, mischaracterize the main concerns of our report, and supply inaccurate information alleging to refute our concerns. The IALS's views certainly do not represent any consensus of the scientific community. In fact, two recent reports by the National Academy of Sciences[1] question the wisdom of using food crops to produce pharmaceuticals, as do the editors of the respected journal *Nature Biotechnology*[2] and a growing number of scientists. In addition, the Grocery Manufacturers of America, the National Food Processors Association, and other trade groups representing America's largest food and food processing companies have strongly objected to the use of food crops as a vehicle for outdoor production of experimental pharmaceuticals.[3] Like us, they are rightly concerned about the potential hazards of this irresponsible practice.

Despite its appeal to science, IALS makes numerous unsupported or inaccurate assertions and lists only one citation in support of its arguments (in contrast, our report is thoroughly referenced with citations to many peer-reviewed papers from the scientific literature and regulatory sources). We address these errors and mischaracterizations in

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[1] National Research Council of the National Academy of Sciences (2002). "Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation," National Academy Press, p. 68. http://books.nap.edu/catalog/10258.html. National Research Council of the National Academies of Science (2004). "Biological Confinement of Genetically Engineered Organisms," National Academy Press, p. 7. http://www.nap.edu/catalog/10880.html.

[2] "Drugs in crops – the unpalatable truth," Editorial, *Nature Biotechnology* 22(2), Feb. 2004; "Going with the flow," Editorial, *Nature Biotechnology* 20(6), June 2002.

[3] "No Use of Food or Feed Crops for Plant-Made Pharmaceutical Production Without A '100% Guarantee' Against Any Contamination , Says NFPA," Press Release, National Food Processors Association, Feb. 6, 2003. http://www.nfpa-food.org/News_Release/020603NewsRelease.htm.

the first attachment. First, however, we discuss IALS's vastly exaggerated case for the feasibility of plant-made pharmaceuticals.

The companies engaged in "biopharming" are mostly start-up biotech firms with no marketable products. In order to raise money from investors and government funding agencies, they often exaggerate the prospects of their research projects. Numerous biopharm start-ups heralding imminent cures or treatments for cancer, HIV, heart disease, etc. (as the IALS does in its letter) have declared bankruptcy or have been acquired by other companies without producing anything. A short list includes ProdiGene, CropTech, Epicyte Pharmaceutical and Axis Genetics. Monsanto shut down its pharm crop division last year due to the bleak prospects in this sector. The State of Iowa recently spent $6 million scarce public dollars to subsidize ProdiGene; the only return on its investment was an expensive contamination incident that required 155 acres of potentially contaminated corn to be burned. CropTech in Virginia spent over $12 million in federal government subsidies and state tobacco settlement funds before going bankrupt. Large Scale Biology's stock has dropped 95% in value since going public in 2000. Most recently, Epicyte Pharmaceutical of San Diego, once an acknowledged leader in the development of pharmaceutical corn, was acquired by Biolex of North Carolina. Epicyte's closure is the latest in a string of biotech failures that have thwarted San Diego's ambition of becoming the "Silicon Valley of agricultural biotech."[4] Significantly, Biolex is not interested in food crop biopharming, but rather is pursuing the more responsible course of generating biopharmaceuticals in contained facilities employing a genetically engineered aquatic plant.[5]

We particularly object to IALS's misleading statements as they apply to plant-made vaccines for high-profile diseases. Efforts to develop an AIDS vaccine in plants are a case in point. It is true that an experimental AIDS vaccine based on the gp120 envelope protein derived from the simian version of HIV (SIV) has been developed in corn by ProdiGene, Inc. While to our knowledge this plant-based vaccine has not been clinically tested, gp120 vaccines produced by other means have an abysmal record of failure in numerous clinical trials. In a recent article in *Science*, 18 leading AIDS researchers strongly objected to further human trials, stating: "The gp120 component has now been proven in phase III trials in the United States and Thailand to be ***completely incapable of preventing or ameliorating HIV-1 infection***" (emphasis added).[6] And there is no reason to think the plant-produced counterpart will fare any better. Other researchers are concerned that gp120 could actually suppress an effective immune response to HIV or lead to emergence of more virulent strains of HIV.[7] One team has called for a moratorium on gp120 vaccine development.[8] Indeed, even ProdiGene admits

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[4] Crabtree, P. "Epicyte Pharmaceutical joins failing-biotech row," San Diego Union-Tribune, May 7, 2004. http://www.signonsandiego.com/news/business/20040507-9999-1b7epicyte.html.

[5] "Biolex Acquires Epicyte Pharmaceutical," Biolex press release, May 6, 2004. http://www.biolex.com/pdfs/Biolex%20Acquires%20Epicyte.pdf

[6] Burton et al (2004). "A sound rationale needed for phase III HIV-1 vaccine trials," *Science* 303, January 16, 2004, p. 316.

[7] Koehler et al (2002). "No hope for an AIDS vaccine soon," *AIDScience*, Vol. 2, No. 5, March 2002.

[8] Veljkovic et al (2001). "AIDS epidemic at the beginning of the third millennium: time for a new vaccine strategy," *Vaccine* 19(15-16), 1855-1862.

that its gp120 will probably never become an effective oral AIDS vaccine, viewing it instead as a "proof-of-concept" (demonstration project) for its general objective of developing a "vaccine delivery system."[9]

While we do not question the sincerity and good intentions of the IALS letter's authors (as they do ours), it does not serve the public interest to make exaggerated claims and raise false hopes concerning this dubious technology. Such investor- and media-directed hype has the unfortunate effect of diverting limited R&D funds and investment capital from more promising drug development techniques. The record is clear. Despite 14 years of outdoor field trials, biopharming has yet to produce even one FDA-approved pharmaceutical or vaccine. Compare this record of failure to the more than 100 FDA-approved biopharmaceuticals produced in contained and controlled pharmaceutical factories that are currently helping people in need. This may help explain why one of the world's largest producers of biopharmaceuticals, Novartis Pharma, is skeptical of the plant platform and instead recently committed $6 billion to further development of these proven, controlled and contained systems.

While we support responsible research into new ways to produce needed drugs, we believe that biopharming in food crops grown out-of-doors is misguided. Its failure thus far reflects a constellation of obstacles that may well never be overcome: technical difficulties unique to the plant system, lack of control over production conditions in the form of fluctuating environmental conditions, and the legitimate concern of food companies, scientists and consumer groups about the potential health and environmental risks of contamination.

Attachment 1 contains our detailed responses to the errors and mischaracterizations in IALS's letter. Attachment 2 contains a partial history of transgenic contamination episodes. We have also enclosed an analysis of the biopharm sector which further explains the bleak prospects of this technology and documents the assertions not documented in this letter.

We look forward to further discussion with you about these issues.

Sincerely,

Doug Gurian-Sherman, Ph.D. and Bill Freese
Senior Scientist Research Analyst
Center for Food Safety Friends of the Earth

[9] "ProdiGene announces milestone in NIH collaboration for AIDS vaccine," ProdiGene press release, April 9, 2002.

cc: Terry Tamminen, California Environmental Protection Agency; Secretary A.G. Kawamura, California Department of Food and Agriculture

Enclosures

Attachment 1

Response to Errors and Misrepresentations in IALS's Critique of *Pharmaceutical Crops in California: Potential Risks to Consumers, the Environment and the California Rice Industry*

Most fundamentally, our report does not confuse hazard and risk, as the IALS letter contends. We were careful in our report and communications to the California agencies to point out that our documented concerns are *potential* risk*s*, in other words, hazards or possible hazards that might occur. However, a responsible risk assessment process must either find that such hazards do not exist or that the other important component of a risk equation, exposure to the hazard, either does not occur or is too low to cause significant harm. A basic concern of our report is that the federal regulatory agencies have not performed risk assessments to determine either how serious the identified hazards are, the levels of exposure that may cause harm, or the likelihood that they may occur.

For example, the U.S. Food and Drug Administration has not performed a risk assessment of the possible harm caused by contamination of food by these pharmaceutical proteins. USDA likewise has conducted no environmental risk assessment of these pharmaceutical rice varieties, but rather assumes that contamination will not occur or that it will occur at levels too low to cause harm (again, without supporting risk assessment). Confidence in the prevention of exposure is refuted by the reports by the National Academy cited at the beginning of this letter as well as the history of transgenic contamination episodes (see Attachment 2). Therefore it is incumbent upon the State of California to adequately protect its citizens in the absence of reasonable federal oversight.

The letter from IALS lists several specific points that it contends refute concerns expressed in our report. These points are clearly in error. Some are transparently incorrect, but nonetheless need to be addressed. The most glaring error is to call the proteins expressed in Ventria's rice "human proteins." As the report makes clear, proteins are often more than merely a sequence of amino acids faithfully produced from a gene, because the structure and some properties of the protein typically depend on which organism produces it. Although the proteins in Ventria's rice are expressed from artificial human genes (modified to facilitate expression in plants), because plants and humans typically modify proteins differently, a protein produced from a human-derived gene in a plant will often be different than the protein produced from the same gene in a human. Contrary to the contention of the letter, we acknowledge that the Ventria rice proteins are human-derived. However, the IALS's failure to acknowledge the basic biochemical differences between recombinant plant and human proteins (documented in the case of human versus rice-expressed lactoferrin) reveals a serious lack of understanding of the relevant science and potential risks from biopharm crops.

Some of the possible risks due to differences between proteins produced in plants and humans are discussed in detail in our report. Therefore, we will not reiterate these

concerns here. We note, however, that the regulatory agencies also have recognized the potential importance of these differences by requiring or recommending that possible modifications to transgenic proteins, so called post-translational modifications, are assessed. In general, these assessments have been inadequate or lacking. But the basic concept of assessing possible post-translational modifications is acknowledged.[10] Unfortunately, neither USDA nor FDA has performed an assessment of post-translational modifications in the case of Ventria's pharmaceutical proteins, despite the documented differences between human lactoferrin and rice-expressed recombinant lactoferrin, for example.

Other specific points in the IALS letter are also incorrect or otherwise fail to support their arguments. IALS suggests that dispersal of rice pollen by high winds is not a problem because a recent study calculates that the maximum distance for rice pollen travel is 110 meters. Unfortunately, Ventria's USDA permit for 2004 allows food rice to be planted within 200 feet of its biopharm rice.[11] Therefore, this argument by IALS actually confirms the inadequacy of USDA isolation distance requirements. In addition, the 110 meter distance of the cited Song et al. paper is not a maximum, but only what was detected under the conditions of the experiments performed, which do not represent all environmental conditions. IALS also incorrectly states that there is a 25-mile separation standard in use for pharmaceutical rice in California. Although an earlier proposal to grow 120 acres of biopharm rice in Southern California may have achieved such separation, it was rejected by USDA. In fact, current and previous USDA permits to Ventria allowed cultivation in California rice-growing counties with a mandatory isolation distance of just 20 to 200 feet.[12]

Another inaccuracy in the IALS letter is the claim that farm equipment can only be used for the biopharm crops and can therefore not be a source of food rice contamination. USDA permit guidelines require only that planters and harvesters be "dedicated" to pharmaceutical crop production "for the duration of the tests," after which the equipment can be cleaned for use with food crops. Other equipment need not be dedicated, only cleaned.[13] As noted in the report, cleaning of farm machinery is imperfect, especially the internal areas of equipment such as harvesters.

Several of IALS' criticisms are based on "lack of evidence" arguments. A National Academy of Sciences report[14] previously criticized USDA for making similar types of unsupported arguments, because lack of evidence is not the same as evidence of

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[10] "Mammalian Toxicity Assessment Guidelines for Protein Plant Pesticides," EPA's Scientific Advisory Panel, SAP Report No. 2000-03B, Sept. 28, 2000, p. 14. http://www.epa.gov/scipoly/sap/2000/june/finbtmamtox.pdf.

[11] Animal and Plant Health Inspection Service, USDA, see links under permit number 03-365-01r at: http://www.aphis.usda.gov/brs/ph_permits.html

[12] For permits issued prior to May 2002, when the 100 foot isolation distance and 14 day planting date difference compared nearby food rice, was established, USDA's standard recommended isolation distance for field trials of genetically engineered rice (including pharmaceutical rice) was just 20 feet.

[13] "Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds," Animal and Plant Health Plant Inspection Service, USDA, Federal Register, Vol. 68, No. 46, March 10, 2003, p. 11338.

[14] National Research Council (2002), op. cit.

a lack. For example, IALS suggests that dispersal of rice by birds is unlikely because "there is no documented evidence of biotechnology rice growing in wetlands along the migratory routes of ducks." However, IALS provides no evidence that anyone has looked for biotech rice (or even conventional rice) in such areas, and we have found no such studies in the literature. Therefore, IALS's statement is useless for risk assessment. The known role of birds, and waterfowl in particular, in seed dispersal, supports the need to determine the importance of this route of possible dispersal of biopharm seeds, rather than assuming that it will not occur. The absence of these and other risk assessment studies are a large part of our concern about the inadequate federal regulation of biopharm crops.

IALS's claim that it is unaware of disease resistance traits from cultivated rice that confer a competitive advantage to wild rice is also an unsupported argument. One first should ask whether anyone has studied the effect of these genes in wild rice, and IALS provides no such studies. More importantly, IALS seems to not understand the importance of fecundity in the fitness of plants when it comments that Ventria's proteins are expressed only in the seed, and therefore that no mechanism exists to provide a competitive advantage to wild rice relatives. For example, the American Phytopathological Society lists several diseases of rice kernels, which may affect fecundity.[15] An important study on seed herbivory in Bt sunflower recently demonstrated how resistance to insects by Bt sunflower seeds may give those plants a competitive advantage.[16] In addition, pharmaceutical proteins expressed in rice seeds may deter some seed rots that occur in the soil as well as seedling diseases, providing another possible advantage.

In conclusion, the inaccuracies and superficial analysis found in the letter by IALS only reinforces the need for California to be diligent in assuring that its citizens are provided with adequate risk assessment of biopharm crops. Alternative plants exist and are being developed for the production of biopharmaceuticals, so the argument that food crops are needed for this purpose is spurious, especially since no crop-made drug has yet reached the market.

[15] American Phytopathological Society, "Common Names of Plant Diseases," see: http://www.apsnet.org/online/common/names/rice.asp

[16] Snow, AA, et al. (2003) A Bt transgene reduces herbivory and enhances fecundity in wild sunflowers. *Ecological Applications* 13(2): 279-286

Attachment 2

Partial History of Transgenic Contamination Episodes[17]

Following are just a few of the dozens of episodes in which contamination from GE crops caused seed or product recalls, and/or other problems for farmers and consumers.

May 1997 — Monsanto is forced to recall 60,000 bags of canola seed when it discovers the seed contains unapproved gene-altered DNA, due to contamination from a planting error by a seed producer.

December 1997 — Unapproved GMO sugar beet from a Monsanto test field is sent to a sugar refiner, where it contaminates natural sugar sold for animal feed.

September 2000 — Over 300 food products were recalled due to contamination by a GMO corn (StarLink, produced by Aventis CropScience), not approved for human food. Experts estimated that half of the state's corn – about 1 billion bushels – could be contaminated. Exports of corn to Japan decreased by 44% in one year. StarLink contamination is still being discovered in US corn shipments three years later.

May 2000 — Nearly 15,000 acres of farmland in five European countries are contaminated with unapproved GMO canola when pollen from the unapproved variety blows into a non-GMO seed producers' field. In addition, French authorities reveal that unapproved GMO seeds have contaminated nearly 10,000 acres of corn planted there.

April 2001 — Just months after StarLink contamination is discovered, Monsanto is compelled to recall thousands of bags of canola seed contaminated with a GMO variety not approved for sale to Canada's major export markets. Incineration is planned for over 10,000 acres of fields already planted with the unapproved crop.

July 2001 – Austrian authorities order thousands of acres of corn destroyed when tests show contamination of non-GMO seed by two unapproved GMO corn varieties.

April 2002 — Corn grown in Argentina and sold as corn flour in Europe is discovered contaminated with a GMO variety that is not approved for planting in Argentina or for human consumption in Europe.

September 2002 — A pharmaceutical corn, produced by ProdiGene, contaminates corn and soybean fields in Iowa and Nebraska. 155 acres of corn is destroyed and $3 million worth of soybeans are quarantined at the elevator and destroyed.

April 2002 — Corn grown in Argentina and sold as corn flour in Europe is discovered contaminated with a GE variety that is not approved for planting in Argentina or for human consumption in Europe.

May 2003 — Tests show that biotech crops have contaminated wheat grown in the US, even though GMO wheat is not approved for marketing. Grain industry experts warn that approving GMO wheat could mean the end of US exports to Europe and Asia.

July 2003 — Over 100 farmers in Italy discover that the non-GMO corn seed they planted was contaminated with an unapproved GMO variety.

December 2003 — UC Davis researchers discover that, for seven years, they had been mistakenly distributing for research purposes GMO tomato seed in place of a conventional variety.

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[17] Based on: BRIEFING ON THE PROPOSED PROTOCOL FOR PHARMACEUTICAL RICE, Attachment 2, Submitted to the AB2622 Advisory Board of the California Rice Commission, March 5, 2004, prepared by Californians for GE-Free Agriculture.