



BIOGRAPHICAL MEMOIRS

JOHN EDWARD CASIDA

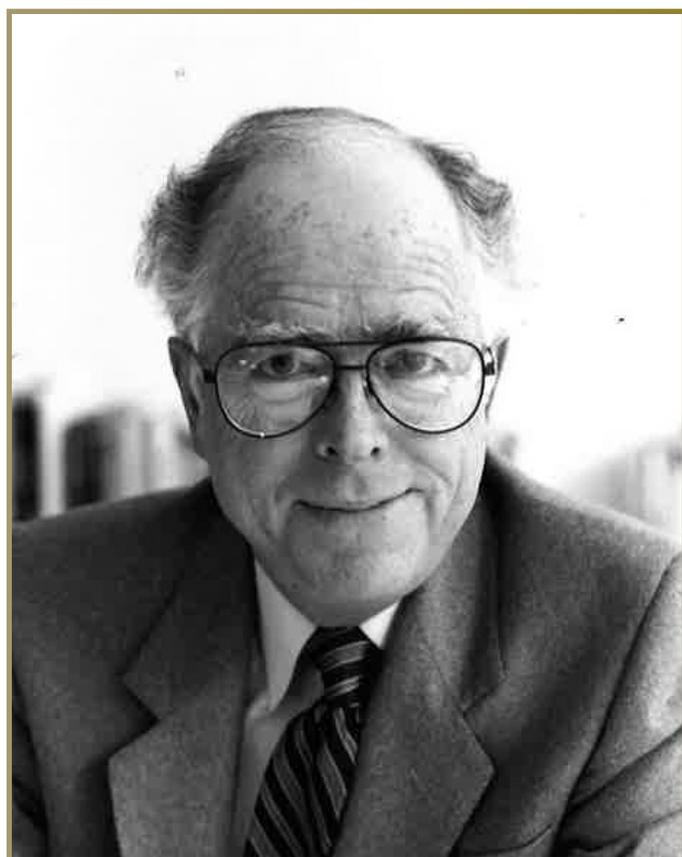
December 22, 1929–June 30, 2018

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*A Biographical Memoir by
Qing X. Li and Bruce D. Hammock*

JOHN E. CASIDA was the pesticide toxicologist of his generation. His profound contributions to our understanding of the toxicology and mechanism of action of most major insecticides, herbicides, and fungicides and their synergists led to more effective agricultural chemicals that are far safer for human and environmental health. He used pesticides as probes for his studies, resulting in great insight into biological chemistry and the underlying mechanisms of selective toxicity and regulatory biology, ranging from voltage-gated sodium channels, the ryanodine receptor, and calcium regulation to the gamma-aminobutyric acid-gated chloride channel and the nicotinic acetylcholine receptors. These discoveries among many others have had a tremendous impact on pharmacology and toxicology.

John Casida was born in Phoenix, Arizona, on December 22, 1929, the first of three children of Ruth and Lester Earl Casida. The Casida family later moved to Conway, Arkansas, and then Columbia, Missouri. In the mid-1930s, Lester Casida received a fellowship to the University of Wisconsin-Madison (UW) and later became a tenured professor there. He spent his career working on the genetics and physiology of reproductive biology. John's mother was a homemaker and was very supportive of her husband's academic aspirations.^{1,2} Life was not easy for the family during this time, but it was an idyllic period for John to become a young biologist because he had free access to the university arboretum, lake, and later the UW entomology department's museum. It was here that he developed a deep love of biological science and collected insects and mites.



John received a bachelor of science in entomology in 1951 from UW. During this period, he took up sabre fencing and became team captain (Figure 1), but he reported that he spent most of his free time in studies and independent research. In 1951, he published his first paper in *Science* on how to evaluate the phytotoxicity and phytostimulation of insecticides when he was twenty-two.³ John then obtained a master of science degree in biochemistry in 1952 and two years later received a joint Ph.D. in entomology and biochemistry under the direction of Mark A. Stahmann and Thomas C. Allen with a minor in botany. With the success of DDT and the rise of organophosphates (OPs) as pesticides after World War





Figure 1 John Casida (middle) and his teammates. Photo taken on December 13, 1949. Photo from the University of Wisconsin at Madison Steenbock library.

II, John became increasingly interested in the interaction of exogenous chemicals with organisms and the impact of pesticides on agriculture and the environment. His Ph.D. work was interrupted by the Korean War and the resulting increase in drafts into the military. Because John was working on OPs, he was offered a direct commission and served as a second lieutenant at the Edgewood Arsenal of the Aberdeen Proving Ground in Maryland working on OP chemicals. When on duty in Costa Rica, John was seriously poisoned with an OP, and this experience certainly spurred an interest in pesticide risks to human health. It is notable that John forgot to tell his fiancée about the incident until he returned from duty. By taking classes during this period and publishing his independent research, he finished his Ph.D. quickly when he returned to Madison in 1954.⁴

His first paper on DDT in 1951 was timely. At the dawn of modern insecticide toxicology, DDT was initially used in World War II to control malaria, typhus, and the other insect-borne human diseases. DDT under a limited exemption is still used today in some countries to control mosquitoes that transmit the parasites that cause malaria. DDT also aided massive increases in crop yields. Rather than only praising the attributes of DDT, John cautioned about the possibly deleterious and unexpected consequences of pesticides in his first *Science* paper.⁵ This ability to see the attributes of pesticides while pointing out cautions regarding their use characterized his whole career. John and Thomas Allen explored in-depth pesticide-related phytotoxicity. These studies led them to expand their interest in OP pesticides, first in plants and then in enzymes in a key paper with Stahmann.⁶

After graduating in 1954, John was offered and accepted an assistant professor position at UW. John became an associate professor in 1957 and full professor in 1961. Three

years later, he was offered the position opened by the retirement of William Hoskins as the toxicologist in the Department of Entomology at the University of California, Berkeley (UCB). He later was awarded the Hoskins's Chair in Chemical and Molecular Entomology, which he held from 1996 until 2018. After his retirement in 2008, he was the Edward A. Dickson Emeritus Professor and Professor of the Graduate School at UCB.⁷

The year 1956 was a pivotal one in John's personal life: he married well-known artist Katherine "Kati" Faustine Monson, who was born in 1931 to a Norwegian-American family in Viroqua, Wisconsin. John and Kati had their first son, Mark, in 1957 and second son, Eric, in 1960. In 1964, John and his family moved to Berkeley. John was an avid shutterbug and an antiquarian of Russian Icons and pre-Columbian pottery from Central and South America. Their house resembled an art gallery. The floor of one of the rooms was covered with signatures of the lab alumni. John and Kati and, for a time, their two sons lived in the Berkeley Hills northeast of campus. John said the walk to and from work gave him time to think. However, when Kati drove up to his basement window of Wellman Hall, John never hesitated to rush out to join her. His advice to the students in his laboratory was, "Never keep Kati waiting." John occasionally joked about his wife's creative eccentricities and "complained" about moving Kati's often large and heavy sculpture installations around the world. He quickly added that she made him a whole human. Kati and John completed each other. They were immersed in the Berkeley art scene and dedicated to culture and Greek dancing. Kati was fully engaged in John's career and interests as he was in hers. Among other things, Kati sent unique Christmas letters on the Casida family and laboratory alumni (Figure 2).

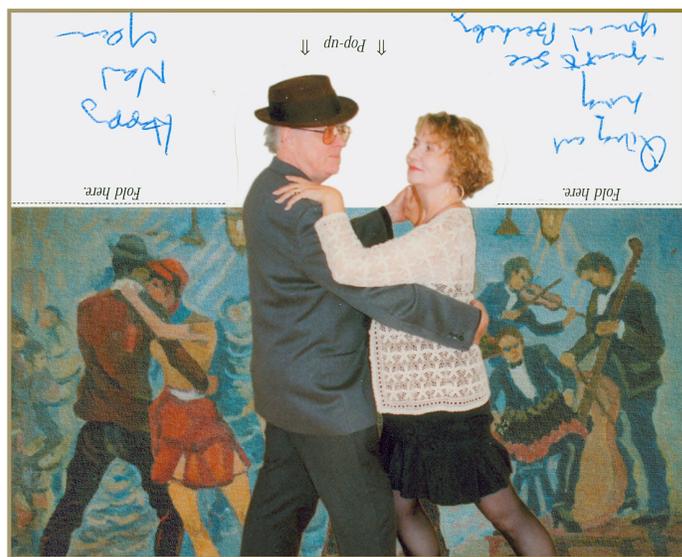


Figure 2 John and Kati Casida, a seasonal greeting card John and Kati sent in December 1999. Qing Li collection.

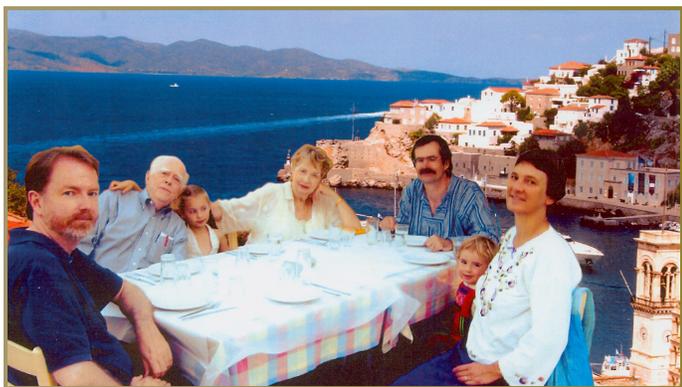


Figure 3 Family photo taken in 2006 at John and Kati's 50th wedding anniversary celebration on the Greek Island of Hydra, a seasonal greeting card John and Kati sent in December 2006. From left to right: Eric (son), John, Mariposa (granddaughter), Kati (wife), Mark (son), Tenaya (grandson), and Mark's wife, Kim (daughter-in-law). *Qing Li collection.*

Sadly, Kati died in 2021. They leave behind their two sons Eric (BeRex Corporation, Berkeley) and Mark (Professor of Theoretical Chemistry, Grenoble-Alps University, Grenoble, France) and Kim Collins Casida (Mark's Wife) and their two grandchildren, Mariposa and Tenaya Casida (Figure 3).

Throughout his career at UCB, John held court in an office at the north end of a long corridor in the lovely but old Wellman Hall on the Berkeley campus. The basement space in this historic building was ample but certainly illustrated that the quality of the space does not make the science. It was notable for chemistry laboratories without emergency showers and only one exit as well as for a room for new graduate students with such a low ceiling one could not stand up. It was here that John founded the Pesticide Chemistry and Toxicology Laboratory (PCTL), later renamed the Environmental Chemistry and Toxicology Laboratory (ECTL), which continued long after his retirement and was finally largely closed only two years before his death.⁸ Even then, John continued research in two small laboratories by his office, with some research published posthumously. John always credited Berkeley the city and Berkeley the campus for his wonderful personal and professional life. He once said Berkeley is not so much a place as a spirit and a time.⁹

John was an avid teacher for his entire career (Figure 4).¹⁰ Generations of associates and visitors have commented that the most stimulating instruction was on the blackboard in his office. As the author (Hammock) recalled, Sarjeet Gill and I both expressed an interest in working on Carroll Williams's third-generation pesticides, which had recently appeared in *Scientific American*. John thought this was outside the mandate of his NIEHS funding but managed to find us a project. He called us into his office, closed the door, and drew a terpenoid structure on the chalk board. He said it was an experimental insecticide from Stauffer, and we were not to

disclose the structure. I was assigned to radiolabel it and Sarjeet to do its metabolism. We walked down the hall to the first blackboard we found and tried to reconstruct the molecule from our joint memories. We actually were not very close, but it was weeks before we had the courage to ask John to repeat the structure. In addition to his weekly lab meetings, John always periodically scheduled time with each team member to update their research progress. He mostly asked inspirational and intriguing questions. Another great learning opportunity was sitting next to John in his office for manuscript revisions. He always went through the manuscript word by word and sentence by sentence. For most of John's career, he had a semiformal bag lunch, termed "the gripe session," with all laboratory personnel presenting their work on a rotating basis in a tiny windowless room under the slanted roof of Wellman Hall. Casida taught multiple courses but his most notable was a three-credit course on pesticide chemistry and toxicology that he began at UW and continued at Berkeley. He finished grading the final exam of 72 students just several weeks before his death.

John emphasized the concept of selective toxicity in his research and his teaching. He was a key early investigator in the first two important classes of modern insecticides: OPs and N-methylcarbamates. This is demonstrated by his remarkable and prolific research on OPs and carbamates, with approximately 170 insightful OP and 60 carbamate papers. His OP work started in the early 1950s and peaked twice from the 1950s to the 1970s and the 2000s to the 2010s. His first carbamate paper was published in 1958.¹¹ He became increasingly productive in the carbamate field in the 1960s. His work on the two classes of insecticides spanned from structure-activity relationship, metabolism, mode of action, mechanism of action to selective toxicity. This coincided with a "swords to plowshares" transformation of the OP chemical



Figure 4 John and Kati Casida (back right and front left, respectively) with John's former graduate students Sarjeet Gill (back left) and his wife (Lean Gill, front middle), and Bruce Hammock (back middle) and his wife (Lassie Hammock, front right). This photo was taken in 2012. *Bruce Hammock collection.*

warfare agents from World War II into some exceptionally important tools in agriculture and vector biology. The pesticide metabolism field prospered under his leadership with an initial focus on OPs and then the new carbamate class of insecticides. OP esters remain major insecticides, with approximately 150 compounds used for protecting crops, livestock, and human health in the past seventy years or so, whereas there are approximately only 40 N-methylcarbamate insecticides. John's work revealed the selective toxicity of OP insecticides based on specificity differences in the acetylcholinesterase (AChE) targets, more rapid detoxification in mammals than in insects, and the use of proinsecticides undergoing preferential activation in insects as compared with mammals.¹² AChE is the primary target of OP insecticides and chemical warfare agents. OPs cause more cases of human poisoning than any other class of pesticides. John spent years uncovering non-AChE systems.¹³ His research ties together OP pesticides, Gulf War syndrome, and attention deficit/hyperactivity disorder and expanded understanding of fundamental neurobiology. A seminal mouse model developed in his laboratory provided a much-needed system for studies of potential clinical syndromes caused by OP exposure.¹⁴ His studies identified the relevance of lysophospholipase in the mouse brain to OP neuropathy.¹⁵ His team discovered high sensitivity of the cannabinoid CB1 receptor OP toxicants and linkages between monoacylglycerol lipase inhibition by OPs and the associated hypomotility in mice. His studies established that teratogenic effects of OP and methylcarbamate insecticides in avian embryos involved phosphorylation of arylformamidase. Serine hydrolase KIAA1363 and acylpeptide hydrolase are amongst many OP insecticide secondary targets identified in the Casida laboratory.

In the mid-1960s, John expanded his collaborators to some of the leading world figures. In 1966, John and Izuru Yamamoto published the radiosynthesis of the natural pyrethrins and early pyrethroids that initiated possibly his major contribution to the development of practical insect control.¹⁶ This returned John to the sodium channel as the site of action for both DDT and pyrethroids and the importance of xenobiotic metabolism, highlighting esterases and cytochrome P450 (CYP) enzymes. This work led to a lifelong collaboration and friendship with Yamamoto and decades of collaboration with the Rothamsted Experimental Station (now Rothamsted Research) in the United Kingdom, and particularly Michael Elliot.^{17,18} His laboratory both hosted and created the leaders in the pyrethroid field, and probably his hosting of this cadre of scientists led in part to the expansion of the field to dominate insect pest control for decades. The metabolism and photostability studies of these complex molecules were exploited through innovative chemistry first at Rothamsted and then in multiple laboratories around the world to make

pyrethroids the world's dominant class of insecticides and dramatically increase the safety of insecticides.¹⁹ His fundamental research reported in more than 140 papers on the chemistry, stereochemistry, photolysis, metabolism, structure-activity relationship, and mode of action of pyrethrum and pyrethroids ultimately have had a major influence on pyrethroid discovery, development, and safety evaluations. Related investigations demonstrated that important insecticide synergists act as both substrates and inhibitors for microsomal CYP-dependent mixed-function oxidases, thereby blocking detoxification of pyrethroids and other insecticides, prolonging their persistence, and increasing their potency and cost effectiveness. John's contribution to the advance of pyrethroids is of critical importance for control of vectors of West Nile virus and malaria, which result in approximately 300 million cases and one million deaths per year of children in Sub-Saharan Africa. In addition to pyrethroids, John elucidated the mode of action and action site of the botanical insecticide rotenone on nicotinamide adenine dinucleotide dehydrogenase as well as its metabolism and photosensitization.²⁰

In the early 1970s, John extended his OP insecticide work to OP fire retardants and related natural products, which led to an unexpected discovery of bicyclic phosphates and trioxabicyclooctanes with a totally unexpected mode of action.²¹ Two new classes of potential insecticides were speculated to target the central nervous system and subsequently identified to bind tightly to the GABA type A receptor (GABA_AR). This serendipitous study led to some of John's most cited papers and provided great benefit to popular radioligand probes used in many neurobiology laboratories worldwide. The probes include [³H]ethynylbicycloorthobenzoate ([³H]EBOB), [³⁵S]tert-butylbicycloorthobenzoate ([³⁵S]TBOB) and [³⁵S]tert-butylbicyclic phosphorothionate ([³⁵S]TBPS).²² The binding sites of TBPS, TBOB, and EBOB were discovered to be the same as, or closely coupled to, that of the polychlorocycloalkane insecticides, such as dieldrin, lindane, and toxaphene, so finally establishing their mode of action after three billion pounds in weight had been used. He found similar results in collaborative research with his alumni for the rodenticide tetramethylenedisulfotetramine (TETS).²³ His team also elucidated the GABA_AR as the action target of new classes of insecticides, such as fipronil, and many natural products. A related study that John particularly enjoyed was the elucidation of the action mechanism of the spirit absinthe. "Because of this study," quipped John, "I had brief notoriety among the artistic community while before I had been viewed as just the eccentric companion of Kati Casida." John credited a degree of serendipity for his discoveries. Although being in the right place at the right time is always a major driver in science, John seemed to realize when he was at the right time and place.

John described one of his friends and colleagues once by saying, “He has yet another paper in *Science*. That guy has been so lucky for so long, one begins to think he may be good.” John’s statement seems to apply equally to his own career.

In 1975, a paper described how dichloroacetamides protect corn from thiocarbamate herbicide injury without affecting the sensitivity of weeds.²⁴ This discovery initiated the field of herbicide chemical safeners and led to practical applications of chemical safeners to selectively manage weeds. The dichloroacetamide safeners induce the crop-specific synthesis of glutathione and glutathione S-transferases that rapidly detoxify the metabolically activated herbicide, which shed light on discovery of new biochemical targets and identification of metabolic pathways of herbicides.²⁵

John had eminent early contributions to discovery of juvenile hormone mimics and chitin synthesis inhibitors for pest insect management.^{26,27} His juvenoid studies were centered on metabolisms and the structure-activity relationship. In 1978, investigations of the potent benzoylphenyl urea class of chitin synthesis inhibitors took place in his laboratory and described the quick and direct action of diflubenzuron analogs within the insect integument to block the terminal polymerization step in chitin formation.²⁸ This discovery paved the path to developing fungal and insecticidal chitin synthesis inhibitors. This work solidified the concept of “green pesticides” acting on targets that were unique to insects.

In 1984, John’s team isolated and characterized a major insecticidal constituent of the botanical insecticide Ryania and then synthesized the ligand [³H]ryanodine.²⁹ His team soon established the toxicological significance of the Ca²⁺-ryanodine receptor complexes in muscle contraction, which led to the discovery of ryanoid insecticides.³⁰ The current global market of ryanoid insecticides, including flubendiamide, cyantraniliprole, and chlorantraniliprole, has reached approximately USD\$2 billion (about 14 percent of the total insecticide market). The impact of having the ryanodine receptor ligands also revolutionized understanding of calcium regulation and led to a number of therapies ranging from heart disease to convulsions.³¹

Neonicotinoids have been important insecticides to control insect pests on crops since the 1990s. John’s more than sixty papers on them encompassed neonicotinoid metabolism, agonistic action, selective toxicity, photoaffinity probes, and structure-activity relationships. Neonicotinoid insecticide toxicology was an interest for much of his career and was a significant part of his research.³² John’s studies clearly defined the neonicotinoid’s target site, identified its many toxic metabolites and enzymes responsible for the metabolism, and elucidated its special structural features and basis for neonicotinoid safety.³³ His studies well defined the low affinity of neonicotinoids for vertebrate relative to insect

nAChRs as a major factor in their favorable toxicological profiles as insecticides. His studies provided essential knowledge for safe use of neonicotinoid insecticides, and he cautioned their non-target effects and potential impacts on non-target species, such as bees, birds, and pollinators. John’s emphasis on the difference between insect and mammalian nAChRs associated with the action of selective agonists and the safe use of neonicotinoid insecticides illustrates the theme of selective toxicity that dominated his career.

John’s leadership role in advancing use of radioisotopes in biology and particularly in metabolism of agricultural chemicals soon led his laboratory to becoming the state of the art in the field.³⁴ He set the standard of excellence for metabolism studies until good laboratory practices requirements necessitated that the field largely move into commercial laboratories. Metabolism investigations progressed from the OPs, to carbamates, to pyrethroids revealed essential functions and roles of CYP enzymes in selective toxicity. CYP screening is early in the evaluation process now of all pharmaceuticals and pesticides. Shortly thereafter John began applying his technologies in metabolism chemistry³⁵ to environmental degradation and the use of photosensitizers to accelerate degradation of pesticides.³⁶ This also opened the door to fundamental studies in photochemistry of great relevance to environmental chemistry.³⁷ It was during this period that John saw the power of mass spectrometry in metabolism studies and increasingly from this period on high resolution nuclear magnetic resonance (NMR) and mass spectrometry played a massive role in his research.³⁸ Elucidation of the metabolic basis for selective toxicity and environmental fate of OPs, methylcarbamates, pyrethroids, and neonicotinoids were among the major accomplishments of John’s laboratory. His team probed insect nAChR interactions in vivo with neonicotinoid, organophosphorus, and methylcarbamate insecticides, which furthered understanding of the action of these three principal insecticide chemotypes. His contributions have served as a rational basis for the evaluation of the risks and benefits of pesticides and toxicants. The findings have laid a solid foundation for risk assessment of the studied pesticides, particularly when molecular action mechanism and “the risk cup” are considered. The analogy of a “risk cup,” which is envisioned as container of overall exposure to toxins in a lifetime, is used to describe aggregate exposure estimates. The U.S. Environmental Protection Agency uses the risk cup as a conceptual approach to determine the “cumulative risk” posed by the groups of pesticides with common mechanisms of action.

In 2014, his team reported the mechanism by which dithiocarbamate fungicides such as benomyl and their metabolites induce a Parkinson’s disease (PD)-type neurodegeneration in mice and the possible relevance of these

changes to human PD.³⁹ Benomyl exposure in primary mesencephalic neurons inhibits aldehyde dehydrogenase and alters dopamine homeostasis. An epidemiology study supports the association of benomyl exposure with increased PD risk. This aldehyde dehydrogenase model for PD etiology helps explain the selective vulnerability of dopaminergic neurons in PD and provides a potential mechanism through which environmental toxicants contribute to PD pathogenesis.⁴⁰

During the 2010s, the university began withdrawing space and resources from his program, making it harder to run a major research laboratory and compete as one of the longest ever continually funded NIH programs (more than fifty years). Thus, John turned even more attention to his teaching and to writing reviews and perspectives on the field. Between 2015 and 2018, he published more than a dozen reviews and perspectives that lit a path toward fruitful and significant research in the fields. Those reviews and perspectives covered pesticide toxicology, ryanodine receptor, and GABA_A insecticides,⁴¹ novel metabolic reactions and secondary targets of pesticide action,⁴² prodrugs and propesticides, OP toxicology,⁴³ radioligands,⁴⁴ pesticide detoxification,⁴⁵ lipases, and neonicotinoids and other insect nicotinic receptor competitive modulators. By the time of his passing, he was outlining several subsequent reviews in pesticide toxicology.

In this memoir only a few of the many contributions of the Casida laboratory and John's collaborators were addressed. These were selected in large part to illustrate our perception of John's approach to research. Some of these areas remained lifelong but minor interests of John's but never had the recognition to attract funding. Other areas probably are evidence of John "tasting" a new field for possible future interests. Many of the fields he tasted went on to become major research endeavors, often led by the alumni of his laboratory. The authors apologize for the many topics and scientists not mentioned here. Perhaps it is a consolation that the authors themselves during their time in the Casida laboratory were confined to what he referred to as "low priority projects" not covered in this remembrance. Yet these low priority projects shaped both of our subsequent careers. John was well known for his ability to match scientific talents with scientific questions. There is no space to discuss the cross-fertilization of ideas among fields, and our attempt has been just to exemplify John's extraordinary ability to focus on the most important and exciting science with enthusiasm, originality, and success.⁴⁶ Of particular note not covered adequately here is the amplification of his legacy through the numerous scientists that he trained. As compounds and authors are mentioned here, they stimulate in the authors' multi-dimensional memories of inspired leadership and innovation from John, exciting interaction, lovely colleagues, occasional

shenanigans, and good time spent in the laboratory.⁴⁷ Casida alumni of multiple generations gather at meetings to remember the scientist, the person, and the legacy of his inspiration.

Few scientists have had an impact on a field which rivals that of John Casida. This impact goes far beyond the publications, patents, and lectures. Probably his greatest legacy is the many scientists who passed through his laboratory—each with their own story. This is technology transfer at its best. In the fall of 1969, the author (Hammock) was wandering the campus trying to find the Casida lab. To look for Professor Casida, I finally entered the basement of Wellman Hall and found a man in a white coat looking in foul-smelling wooden cabinets filled with bottles. When I asked if he could tell me where to find John Casida, he replied that he would help and continued his methodical search of the cabinets. We slowly worked our way down the hall, where he entered an office, sat behind a desk, and said, "You have found him." Shocked, I replied that I had come to work for him as a grad student. There were a series of rapid-fire questions, such as "why did you not write to me?" Ultimately, they led to "graduate students are not cost effective, space effective, or a good use of my time." As I crawled out of Casida's office, I ran into a guy who asked rhetorically, "Are you going to let him scare you off so easily?" I of course said no, Sarjeet Gill became my lifelong friend, and months later John dropped by the table Sarjeet and I shared to ask, "Is there anything I can do to get rid of you two?" With a duet of no, Sarjeet and I acquired a wonderful mentor, an inspiration, and a friend. Fortunately for our field, such events occurred over decades of John holding court in Wellman Hall. It is noteworthy that John had perfectly emulated his father's graduate teaching philosophy: "The emphases in graduate training are to be placed somewhat equally on three things: (1) a sound understanding of the principles underlying the various aspects of science; (2) mastery of some of the techniques for gaining new information, coupled with some understanding of how to develop and learn new techniques; (3) the development of an integrating philosophy of research, experimentation and origin of new knowledge."

John's research was dynamic, well extended, and in-depth. It spanned practical agriculture, classical entomology, fundamental toxicology, basic biology, and biochemistry. John was creative and productive by any measure with more than thirty patents and 800 peer-reviewed publications that have been highly cited in diverse fields.⁴⁸ Because of the breadth of his interests, some scientists have considered John a dilettante, jumping from one exciting area to another. But John's career shows him always moving from one strength to another, showing a clear continuum of science extending from his early career.⁴⁹ The broad swath shows his methodical approach on how best to invest his multiple talents in research.⁵⁰ This



Figure 5 John Casida (6th from front right) and Insect Toxicology 2000 conference attendees. Photo taken on Berkeley campus on July 19, 2000. Qing Li collection.

approach certainly worked for John and for the scientific endeavor. John facilitated an intellectual ferment that extended far beyond his own laboratory and continued in the careers of many of his alumni (Figure 5). John received many awards and honors in recognition of his scientific accomplishments. Among them were his election to the U.S. National Academy of Sciences in 1991, the Royal Society (U.K.) in 1998, and the European Academy of Sciences in 2004. John was awarded the Wolf Prize in Agriculture in 1993, American Chemical Society (ACS) International Award for Research in Pesticide Chemistry in 1969, ACS Kenneth A. Spencer Award for Research in Agricultural and Food Chemistry in 1978, USDA Distinguished Service Award for Research in 1988, and ACS/USDA Sterling B. Hendricks Memorial Lectureship in 1992. He also received the Founders Award from the Society of Environmental Toxicology and Chemistry in 1994 and the Distinguished Service Award from the American College of Toxicology in 2009.

John was a gifted scientist, and he is seen as an icon of his generation. John pioneered studies on the toxicology and mode of action of most significant insecticides, herbicides, and fungicides. In addition to the discovery that ryanoid and cyclodiene insecticides disrupt the calcium and chloride channels, areas of study include research on the synthesis, metabolism, toxicokinetics and mechanisms of toxicity of the organophosphates, pyrethroids, and neonicotinoids. His colossal contributions to multiple disciplines fostered subsequent science. The scientists he mentored are one of his legacies.⁵¹ John set a high standard of ethics as well as work ethics in the field. What drives any of us, and particularly

John Casida? Clearly wealth and fame were not important drivers, but there was a competitive spirit. The success of his many alumni brought him pleasure. We are sure John appreciated the tremendous contribution his career made to environmental and human health issues as well as agriculture. His laboratory was filled with international students. In talking to numerous Casida alumni, the conclusion was that he did it all for the fun of science.⁵² He was curious about science, noting “A scientist is a child who grows up without losing his curiosity.” His immense achievements will be richly remembered.

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REFERENCES

- Hammock, B. D., and Q. X. Li. 2022. John Edward Casida. 22 December 1929–30 June 2018. London: The Royal Society; <https://royalsocietypublishing.org/doi/10.1098/rsbm.2022.0016>.
- Inskeep, K., R. Cochrane, R. Dailey, and F. Stormshak. 2022. The seminal contributions of Lester Earl Casida to reproductive biology: Experimental design, interpretation, integrity (1904–1986). Reston, Va.: Society for the Study of Reproduction; <https://www.ssr.org/about/our-history/memorial.html>.
- Casida, J. E., and T. C. Allen. 1951. A laboratory method for evaluating the phytotoxicity or phytostimulation of insecticides. *Science* 113:553–555.
- Rice, M. E. 2019. John E. Casida: Fabulously toxic. *Am. Entomol.* 65(1):6–12.
- Casida, J. E., and T. C. Allen. 1951.
- Casida, J. E., T. C. Allen, and M. A. Stahmann. 1953. Enzymatic and chemical oxidation of dimethyl-phosphoramides to biologically active dimethyl-phosphoramidate oxides. *Nature* 172:243–245.
- Nomura, D. K. 2018. Virtual issue on the work of John Casida. *Chem. Res. Toxicol.* 31:637–638.
- Quistad, G. 2000. Environmental Chemistry and Toxicology Laboratory, University of California at Berkeley. *Pestic. Outlook* 11:135–137.
- Hammock, B. D., and Q. X. Li. 2022.
- Garvey, K. K. 2018. Remembering world-renowned toxicologist John Casida of UC Berkeley. *Entomology & Nematology News*, July 17, <https://ucanr.edu/blogs/blogcore/postdetail.cfm?postnum=27747>
- Mengle, D. C., and J. E. Casida. 1958. Inhibition and recovery of brain cholinesterase activity in house flies poisoned with organophosphate and carbamate compounds. *J. Econ. Entomol.* 51:750–757.

REFERENCES (CONT.)

- 12 Casida, J. E. 2017. Organophosphorus xenobiotic toxicology. *Annu. Rev. Pharmacol.* 57:309–327.
- 13 Casida, J. E. 2016. Unexpected metabolic reactions and secondary targets of pesticide action. *J. Agric. Food Chem.* 64 (22):4471–4477.
- 14 Winrow, C. J., et al. 2003. Loss of neuropathy target esterase in mice links organophosphate exposure to hyperactivity. *Nat. Genet.* 33:477–485.
- 15 Quistad, G. B., C. Barlow, C. J. Winrow, and S. E. Sparks. 2003. Evidence that mouse brain neuropathy target esterase is a lysophospholipase. *Proc. Natl. Acad. Sci. U.S.A.* 100:7983–7987.
- 16 Yamamoto, I., and J. E. Casida. 1966. O-demethyl pyrethrin II analogs from oxidation of pyrethrin I, allethrin, dimethrin, and phthalthrin by a house fly enzyme system. *J. Econ. Entomol.* 59:1542–1543.
- 17 Pickett, J. 2016. Michael Elliott CHE. *Biogr. Mem. Fellows R. Soc.* 62:109–123.
- 18 Yamamoto, I. 2018. John Edward Casida (1929–2018). *Pestic. Sci.* 43(4):321–324.
- 19 Berteau, P. E., J. E. Casida, and T. Narahashi. 1968. Pyrethroid-like biological activity of compounds lacking cyclopropane and ester groupings. *Science* 16:1151–1153.
- 20 Ivie, G. W., and J. E. Casida. 1970. Enhancement of photoalteration of cyclodiene insecticide chemical residues by rotenone. *Science* 167:1620–1622.
- 21 Bellet, E. M., and J. E. Casida. 1973. Bicyclic phosphorus esters: High toxicity without cholinesterase inhibition. *Science* 182:1135–1136.
- 22 Casida, J. E. 2018a. Radioligand recognition of insecticide targets. *J. Agric. Food Chem.* 66 (13):3277–3290.
- 23 C. Zhao, et al. The GABA_A receptor target of tetramethylenedisulfotetramine. *Proc. Natl. Acad. Sci. U.S.A.* 111:8607–8612.
- 24 Lay, M.-M., J. P. Hubbell, and J. E. Casida. 1975. Dichloroacetamide antidotes for thiocarbamate herbicides: mode of action. *Science* 189:287–289.
- 25 Casida, J. E. 2018b. Pesticide detox by design. *J. Agric. Food Chem.* 66(36):9379–9383.
- 26 Hammock, B. D., S. S. Gill, and J. E. Casida. 1974. Synthesis and morphogenetic activity of derivatives and analogs of aryl geranyl ether juvenoids. *J. Agric. Food Chem.* 22:379–385.
- 27 Hajjar, N. P., and J. E. Casida. 1978. Insecticidal benzophenyl ureas: Structure-activity relationships as chitin synthesis inhibitors. *Science* 200:1499–1500.
- 28 Hajjar, N. P., and J. E. Casida. 1978.
- 29 Waterhouse, A. L., I. Holden, and J. E. Casida. 1984. 9,21-Didehydro-ryanodine: A new principal toxic constituent of the botanical insecticide Ryania. *Chem. Comm.* 19:1265–1266.
- 30 Pessah, I. N., A. L. Waterhouse, and J. E. Casida. 1985. The calcium ryanodine receptor complex of skeletal and cardiac muscle. *Biochem. Biophys. Res. Comm.* 128:449–456.
- 31 Casida, J. E. 2015. Golden age of RyR and GABA-R diamide and isoxazoline insecticides: Common genesis, serendipity, surprises, selectivity, and safety. *Chem. Res. Toxicol.* 28:560–566.
- 32 Hammock, B. D., and Q. X. Li. 2022.
- 33 Talley, T. T., et al. Atomic interactions of neonicotinoid agonists with AChBP: Molecular recognition of the distinctive electronegative pharmacophore. *Proc. Natl. Acad. Sci. U.S.A.* 105:7606–7611.
- 34 Casida, J. E. 1961. Use of radioisotopes in insecticide studies. Hearings before the Subcommittee on Research, Development and Radiation of the Joint Committee on Atomic Energy, Congress of the United States, 87th Congress. Applications of Radioisotopes and Radiation in the Life Sciences, First Session, March 27–30, pages 427–438.
- 35 Casida, J. E., E. C. Kimmel, M. Elliott, and N. F. Janes. 1971. Oxidative metabolism of pyrethrins in mammals. *Nature* 230:326–327
- 36 Ivie, G. W., and J. E. Casida. 1970.
- 37 Johnston, J., and L. Ruzo. 2011. Still curious: An overview of John Casida's contributions to agrochemical research. *J. Agric. Food Chem.* 59: 2760–2761.
- 38 Johnston, J., and L. Ruzo. 2011.
- 39 Hammock, B. D., and Q. X. Li. 2022.
- 40 Casida, J. E., et al. 2014. Benomyl, aldehyde dehydrogenase, and the catecholaldehyde hypothesis for the pathogenesis of Parkinson's disease. *Chem. Res. Toxicol.* 27:1359–1361.
- 41 Casida, J. E. 2015.
- 42 Casida, J. E. 2016.
- 43 Casida, J. E. 2017.
- 44 Casida, J. E. 2018a.
- 45 Casida, J. E. 2018b.
- 46 Hammock, B. D., and Q. X. Li. 2022.
- 47 This Flickr collection of images from John's lab from 1984 to 1986 offer perfect examples of the environment he created at the time: <https://www.flickr.com/gp/66011173@N03/7n3E68>.
- 48 Komives, T. 2018. Look for the unusual: In memory of Professor John E. Casida (1929–2018). *Ecocycles* 4(1):65–67.
- 49 Hammock, B. D., and K. F. Casida. 1998. For the fun of science: A discussion with John Casida. *Arch. Insect Biochem. Physiol.* 37:1–7.
- 50 Wing, K. D. 2019. In memory of Professor John E. Casida. *Pestic. Biochem. Physiol.* 161:2–4.
- 51 Hammock, B. D., and Q. X. Li. 2022.
- 52 Hammock, B. D., and K. F. Casida. 1998.

SELECTED BIBLIOGRAPHY

- 1951 With T. C. Allen. A laboratory method for evaluating the phytotoxicity or phytostimulation of insecticides. *Science* 113:553–555.
- 1953 With T. C. Allen and M. A. Stahmann. Enzymatic and chemical oxidation of dimethyl-phosphoramides to biologically active dimethyl-phosphoramidate oxides. *Nature* 172:243–245.
- 1958 With D. C. Mengle. Inhibition and recovery of brain cholinesterase activity in house flies poisoned with organophosphate and carbamate compounds. *J. Econ. Entomol.* 51:750–757.
- 1961 Use of radioisotopes in insecticide studies. Hearings before the Subcommittee on Research, Development and Radiation of the Joint Committee on Atomic Energy, Congress of the United States, 87th Congress. Applications of Radioisotopes and Radiation in the Life Sciences, First Session, March 27–30, pages 427–438.

SELECTED BIBLIOGRAPHY (CONT.)

- 1966 With I. Yamamoto. O-Demethyl pyrethrin II analogs from oxidation of pyrethrin I, allethrin, dimethrin, and phthalthrin by a house fly enzyme system. *J. Econ. Entomol.* 59:1542–1543.
- 1968 With P. E. Berteau and T. Narahashi. Pyrethroid-like biological activity of compounds lacking cyclopropane and ester groupings. *Science* 16:1151–1153.
- 1970 With G. W. Ivie. Enhancement of photoalteration of cyclodiene insecticide chemical residues by rotenone. *Science* 167:1620–1622.
- 1971 With E. C. Kimmel, M. Elliott, and N. F. Janes. Oxidative metabolism of pyrethrins in mammals. *Nature* 230:326–327.
- 1973 With E. M. Bellet. Bicyclic phosphorus esters: High toxicity without cholinesterase inhibition. *Science* 182:1135–1136.
- 1975 With M.-M. Lay and J. P. Hubbell. Dichloroacetamide antidotes for thiocarbamate herbicides: Mode of action. *Science* 189:287–289.
- 1974 With B. D. Hammock and S. S. Gill. Synthesis and morphogenetic activity of derivatives and analogs of aryl geranyl ether juvenoids. *J. Agric. Food Chem.* 22:379–385.
- 1978 With N. P. Hajjar. Insecticidal benzophenyl ureas: Structure-activity relationships as chitin synthesis inhibitors. *Science* 200:1499–1500.
- 1984 With A. L. Waterhouse and I. Holden. 9,21-Didehydroryanodine: A new principal toxic constituent of the botanical insecticide *Ryania*. *Chem. Comm.* 19:1265–1266.
- 1985 With I. N. Pessah and A. L. Waterhouse. The calcium ryanodine receptor complex of skeletal and cardiac muscle. *Biochem. Biophys. Res. Comm.* 128:449–456.
- 2003 With C. J. Winrow, et al. Loss of neuropathy target esterase in mice links organophosphate exposure to hyperactivity. *Nat. Genet.* 33:477–485.
- With G. B. Quistad, C. Barlow, C. J. Winrow, and S. E. Sparks. Evidence that mouse brain neuropathy target esterase is a lysophospholipase. *Proc. Natl. Acad. Sci. U.S.A.* 100:7983–7987.
- 2008 With T. T. Talley, et al. Atomic interactions of neonicotinoid agonists with AChBP: Molecular recognition of the distinctive electronegative pharmacophore. *Proc. Natl. Acad. Sci. U.S.A.* 105:7606–7611.
- 2014 With B. Ford, et al. Benomyl, aldehyde dehydrogenase, and the catecholaldehyde hypothesis for the pathogenesis of Parkinson's disease. *Chem. Res. Toxicol.* 27:1359–1361.
- With C. Zhao, et al. The GABAA receptor target of tetramethylenedisulfotetramine. *Proc. Natl. Acad. Sci. U.S.A.* 111:8607–8612.
- 2015 Golden age of RyR and GABA-R diamide and isoxazoline insecticides: Common genesis, serendipity, surprises, selectivity, and safety. *Chem. Res. Toxicol.* 28:560–566.
- 2016 Unexpected metabolic reactions and secondary targets of pesticide action. *J. Agric. Food Chem.* 64 (22):4471–4477.
- 2017 Organophosphorus xenobiotic toxicology. *Annu. Rev. Pharmacol.* 57:309–327.
- 2018 Radioligand recognition of insecticide targets. *J. Agric. Food Chem.* 66 (13):3277–3290.
- Pesticide detox by design. *J. Agric. Food Chem.* 66 (36): 9379–9383.