

Biorational Control of Arthropod Pests

Isaac Ishaaya • A. Rami Horowitz
Editors

Biorational Control of Arthropod Pests

Application and Resistance Management

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Editors

Isaac Ishaaya
Department of Entomology
Agricultural Research Organization
The Volcani Center
Bet Dagan 50250
Israel
vpisha@volcani.agri.gov.il

A. Rami Horowitz
Department of Entomology
Agricultural Research Organization
Gilat Research Center
MP Negev 85280
Israel
hrami@volcani.agri.gov.il

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Preface

For nearly 50 years, pest control was mostly based on broad-spectrum conventional insecticides such as organochlorines, organophosphates, carbamates and pyrethroids. However, the severe adverse effects of pesticides on the environment, problems of resistance reaching crisis proportions and public protests led to stricter regulations and legislation aimed at reducing their use. Ways to reduce the use of synthetic pesticides in plant protection and to use more alternative and novel methods for pest control or biorational control are the challenges of pest control for the twenty-first century.

The term biorational (biological + rational) pesticides can be defined as the use of specific and selective chemicals, often with a unique modes of action, that are compatible with natural enemies and the environment, with minimal effect on non-target organisms. Biorational control is based on a diversity of chemical, biological and physical approaches for controlling insect pests which results in minimum risk to man and the environment.

Among the highlights of this book are the use of selective control agents acting on specific biochemical sites such as neuropeptides, ecdysteroids and juvenile hormone analogs; GABA, ACh, ryanodine and octopamine receptors; pheromone and insect communication disruption along with plant constituents for selectively controlling arthropod pests. Novel biotechnology strategies that exploit genetically modified plants, insects, and symbionts for the management of insect pests and disease-borne vectors are presented. Furthermore, physical control techniques can serve as important tools to protect our crops from arthropod pests. Finally, countermeasures for resistance to biorational control agents using advanced biological and biochemical approaches are also discussed.

The authors of the various chapters are world expert in fields related to biorational control, have reviewed and collated the widespread literature in a concise and consolidated form. The book is intended to serve as a text for researchers, university professors, graduate students, agricultural organizations and chemical industries.

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Contributors

Alphey, L Oxitec Ltd, 71 Milton Park, Oxford OX14 4RX, UK,
Department of Zoology, University of Oxford, Oxford OX1 2PS, UK,
luke.alphey@oxitec.com

Altstein, M Department of Entomology, The Volcani Center, Bet Dagan 50250,
Israel, vinnie2@agri.gov.il

Bourtzis, K Department of Environmental and Natural Resources Management,
University of Ioannina, 2 Seferi St., 30100 Agrino, Greece, kbourtz@cc.uoi.gr

Čokl, A. A Department of Entomology, National Institute of Biology, Vecna Pot
111, SI-1000 Ljubljana, Slovenia, andrej.cokl@nib.si

Darby, A.C School of Biological Sciences, University of Liverpool, Crown
Street, Liverpool, L69 7ZB, United Kingdom, Alistair.darby@liverpool.ac.uk

Ellsworth, P. C Department of Entomology, University of Arizona, Arizona Pest
Management Center, Maricopa, AZ 85239, USA, peterell@ag.arizona.edu

Franco, J. C Departamento de Protecção de Plantas e de Fitoecologia, Instituto
Superior de Agronomia, Universidade Técnica de Lisboa (ISA/UTL), 1349-017
Lisboa, Portugal, jsantossilva@utl.pt

Hariton, A Department of Entomology, The Volcani Center, Bet Dagan 50250,
Israel, alizav@inter.net.il

Hirashima, A Department of Applied Genetics and Pest Management, Faculty
of Agriculture, Graduate School, Kyushu University, 6-10-1 Hakozaki,
Higashi-ku, Fukuoka 812-8581, Japan, ahirasim@agr.kyushu-u.ac.jp

Horowitz, A. R Department of Entomology, Agricultural Research Organization,
Gilat Research Center, MP Negev 85280, Israel, hrami@volcani.agri.gov.il

Ishaaya, I Department of Entomology, Agricultural Research Organization,
The Volcani Center, Bet Dagan 50250, Israel, vpisha@volcani.agri.gov.il

Matsuda, K Department of Applied Biological Chemistry, School of Agriculture, Kinki University, 3327-204 Nakamashi, Nara 631-8505, Japan, kmatsuda@nara.kindai.ac.jp

Mendel, Z Department of Entomology, Agricultural Research Organization, The Volcani Center, Bet Dagan 50250, Israel, zmendel@volcani.agri.gov.il

Millar, J. G Department of Entomology, University of California, Riverside, CA 92521, USA, millar@ucr.edu

Miller, T Department of Entomology, University of California, Riverside, CA 92521, USA, thomas.miller@ucr.edu

Nachman, R. J Areawide Pest Management Research Unit, Southern Plains Agricultural Research Center, U. S. Department of Agriculture, 2881 F/B Road, College Station., Texas 77845, USA, nachman@tamu.edu

Ozoe, Y Department of Life Science and Biotechnology, Faculty of Life and Environmental Science, Shimane University, Matsue, Shimane 690-8504, Japan, ozoe-y@life.shimane-u.ac.jp

Palli, S. R Department of Entomology, College of Agriculture, University of Kentucky, Lexington, KY 40546, USA, rpalli@uky.edu

Smaghe, G Laboratory of Agrozoology, Department of Crop Protection, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Ghent, Belgium, guy.smaghe@ugent.be

Takeda, M Graduate School of Agricultural Science, Kobe University, 1-1 Rokodai, Nada-Ku, Kobe 675-8501, Japan, mtakeda@kobe-u.ac.jp

Tirry, L Laboratory of Agrozoology, Department of Crop Protection, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Ghent, Belgium, luc.tirry@ugent.be

Tsagkarakou, A National Agricultural Research Foundation (N.AG.RE.F.), Plant Protection Institute of Heraklion, Laboratory of Entomology and Agricultural Zoology, 71003 Heraklion, PO Box 2228, Greece, tsagkarakou@nagref.gr

Van Damme, E. J. M Laboratory of Biochemistry and Glycobiology, Department of Molecular Biotechnology, Ghent University, Coupure Links 653, 9000 Ghent, Belgium, ElsJM.VanDamme@ugent.be

Vandenborre, G Laboratory of Agrozoology, Department of Crop Protection, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Ghent, Belgium, Gianni.Vandenborre@ugent.be

Van Leeuwen, T Laboratory of Agrozoology, Department of Crop Protection, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Ghent, Belgium, thomas.vanleeuwen@ugent.be

Vontas, J Laboratory of Pesticide Science, Agricultural University of Athens, Iera Odos 75, Athens 11855, Greece; Faculty of Applied Biotechnology and Applied Biology, Department of Biology, University of Crete, Vasilika Vouton, 71409 Heraklio, Crete, PO Box 2208, Greece, vontas@imbb.forth.gr

Weintraub, P. G Department of Entomology, Agricultural Research Organization, Gilat Research Center, D.N. Negev, 85280, Israel, phyllisw@volcani.agri.gov.il

Whalon, M Department of Entomology, Michigan State University, East Lansing, Michigan 48824 USA, Whalon@msu.edu

Wise John Department of Entomology, Michigan State University, East Lansing, Michigan 48824 USA, wisejohn@msu.edu

Zada, A Department of Entomology, Agricultural Research Organization, The Volcani Center, Bet Dagan 50250, Israel, anatzada@volcani.agri.gov.il

Biorational Pest Control – An Overview

A. Rami Horowitz, Peter C. Ellsworth, and Isaac Ishaaya

1 Introduction

Fifty years ago, Stern et al. (1959) introduced the concept of “Integrated Control” during a time when insect pest control was mostly based on broad-spectrum, conventional insecticides such as organochlorines, organophosphates (OPs), and carbamates, all neurotoxic. Their work on economic thresholds and economic injury levels implemented within an ecological framework where chemical and biological controls could thrive together is the basis for the modern day Integrated Pest Management (IPM) concept. However, along the way, IPM’s overdependence on these broad-spectrum insecticides led to criticism that IPM was nothing more than Integrated Pesticide Management (e.g. Ehler 2006). Severe adverse effects of pesticides on the environment, problems of resistance reaching crisis proportions, and public protests have driven demand for alternative pest control tactics. With advances in the development of biorational pesticides and other selective chemistries, there is now real opportunity to realize the “Integrated Control” concept that Stern and colleagues (1959) pioneered. Today, more than ever, tools of physiology, toxicology, and biotechnology can help us realize the vision of more holistically harmonizing biological and chemical controls.

A.R. Horowitz (✉)

Department of Entomology, Agricultural Research Organization,
Gilat Research Center, MP Nagev 85280, Israel
e-mail: hrami@volcani.agri.gov.il

P.C. Ellsworth

Department of Entomology, University of Arizona, Arizona Pest
Management Center, Maricopa, AZ 85239, USA
e-mail: peterell@ag.arizona.edu

I. Ishaaya

Department of Entomology, Agricultural Research Organization,
The Volcani Center, Bet Dagan 50250, Israel
e-mail: vpisha@volcani.agri.gov.il

The US Federal definition of IPM underwent a recent paradigm shift towards “risk reduction” as a way of placing focus on the consequences and impacts of pests and pest management tactics rather than just pesticides, per se:

Integrated Pest Management, or IPM, is a long-standing, science-based, decision-making process that identifies and reduces risks from pests and pest management related strategies. It coordinates the use of pest biology, environmental information, and available technology to prevent unacceptable levels of pest damage by the most economical means, while posing the least possible risk to people, property, resources, and the environment. IPM provides an effective strategy for managing pests in all arenas from developed agricultural, residential, and public areas to wild lands. IPM serves as an umbrella to provide an effective, all encompassing, low-risk approach to protect resources and people from pests. Anonymous (2004)

Reducing the risks associated with pest management tactics like pesticides in plant protection is the challenge of pest control for the twenty-first century. Biorational agents and approaches will be the key for elevating our IPM strategies to meet the societal challenges before us (Ishaaya 2003; Horowitz and Ishaaya 2004; Ishaaya et al. 2005).

This volume was written to address the demand for safer, environmentally friendly approaches to pest management, and to describe new strategies to reduce resistance problems. The biological control of pests is not dealt with, but rather control-methods that are compatible with beneficial organisms. This overview is based on the different chapters of this book, which deals with biorational approaches for insect (and mite) pest control. One such approach is based on disrupting the activity of specific biochemical sites such as neuropeptides, ecdysone and juvenile hormones, tyramine, octopamine and GABA receptors. Another is the use of natural products obtained from tropical plants and other biological systems for pest control. The use of semiochemicals and of insect signaling still needs to be improved and commercialized. Novel biotechnology control strategies (“the genetic approach”) exploit genetically modified-plants, -insects, and -symbionts in the combat against insect pests and disease-borne vectors. Countermeasures for resistance to biorational control agents using advanced biological and biochemical approaches are also discussed.

2 The Term ‘Biorational’

Precise use of terminology is very important in communicating concepts to fellow scientists, students of various pest management disciplines, and end-users of pest management technology. However, precise usage of the term “biorational” is difficult, mainly because of its inconsistent use through history. Before presenting an overview of this volume which is dedicated to biorational pest control, a short review of the underlying concepts that have given rise to a plethora of pest control terminology is needed and should be considered along with other thoughtful and authoritative treatments of this and related subject areas (e.g., Crump et al. 1999; Eilenberg et al. 2001; Ware and Whitacre 2004).

Classification systems for pesticides have been proposed along themes of chemical structure (e.g., carbamate, chlorinated hydrocarbon), mode of action, route of entry (e.g., feeding, contact), relative toxicity (e.g., to humans, mammals, vertebrates, fish, or invertebrates), source of origin (e.g., ‘natural’, botanical, analog, or synthetic), process (design model used) and functional role. It is no wonder that attempts to unify these competing and overlapping systems have often met with frustration. However, a continuing push has been made by scientific and public interests to incorporate additional terminology in the development of safer and more sustainable alternative pest control technologies (e.g., ATTRA-National Agricultural Information Service).

Because of their widespread impact on industry and consumers, two major entities, the Internet and US-EPA (2008), influence any discussion about pesticides and pest control technologies even when at odds with more technically precise or scientifically developed terminology. Popular sources associate the term “biorational” as being substances of microbial or plant origin, or having certain physical or contact routes of entry. Some erroneously view biorationals as fully interchangeable with organic pesticides as defined by USDA standards. Others identify biorationals with pesticides of natural origin or that are synthesized identically or as analogs to naturally occurring plant or insect chemicals.

US-EPA does not explicitly define or identify biorationals within their classification system. Ware and Whitacre (2004) attributed erroneously to EPA the view that biorationals are inherently different from conventional pesticides and have lower risks associated with their use. However, this view is what is ascribed by EPA to “biopesticides”, a common but inappropriate synonym for the term biorational (for a review of biopesticides, see Rosell et al. 2008). EPA divides biopesticides, which are “derived from natural materials”, into three groups: “microbials”, plant-incorporated protectants (PIPs), and biochemicals. Microbial pesticides consist of a microorganism such as viruses, bacteria, fungi or protozoa. More broadly, microbial pesticides are generally considered a form of biological control, as they entail the usage of living organisms to induce mortality of target pests (Eilenberg et al. 2001). In addition, some microbials act as antagonists and may not kill the target outright and therefore are better referred to as biopestistats (Crump et al. 1999).

PIPs have come into public consciousness as products of genetic-engineering. EPA regulates the genetic material and its protein products in the plant. The scientific community is divided on how PIPs should be viewed, but many suggest this as a specialized case of host-plant resistance in pest management terminology. EPA’s definition of “biochemical pesticides” is problematic as well under the description that they “...are naturally occurring substances that control pests by non-toxic mechanisms.” In other words they interfere or otherwise alter pest behavior or function, but do not kill the pest outright. They include such things as pheromones and other semiochemicals. As such, these are not pesticides *sensu* Crump et al. (1999).

Crump and colleague’s classification system (1999) is helpful in the organization of many pesticides. However, the major dichotomies in it are whether the substance is “biological” (or living) or “chemical”, and then whether the substance kills the

target or not. While logical, this system is insufficient to accommodate the more subtle functional distinctions that are possible. Crump et al. (1999) also concluded that the diversity of definitions applied to “biorational” leads to confusion. They therefore concluded that the term was “inherently defective” and should be avoided. Yet, given its widespread usage and being the subject of this volume, a more concerted effort is needed to identify and define the concept of biorational and related terms.

A practical desire to avoid prior issues with chemical pesticides, i.e. environmental persistence, food safety, resistance, secondary pest outbreaks, and pest resurgences have deep roots in our pest management culture. Fifty years ago, Stern et al. (1959) dedicated a section in their landmark paper to terminology. They defined “*Selective insecticide*” as:

An insecticide which while killing the pest individuals spares much or most of the other fauna, including beneficial species, either through differential toxic action or through the manner in which the insecticide is utilized (formulation, dosage, timing, etc.)

This extraordinary insight was based in recognition of six key drawbacks of insecticides: (1) arthropod resistance, (2) secondary pest outbreaks resulting from interference of the insecticide with biological control or through its effects on the plant (e.g., hormoligosis), (3) rapid resurgence of the primary target pest because of broad-spectrum decimation of beneficial arthropods and release from biological control, (4) toxic residues in food and forage crops, (5) hazards to insecticide handlers, and (6) litigation arising from all of the above. Today, we could add environmental contamination and regulatory costs associated with the above issues.

Stern et al. (1959) made two other critical observations. Population regulatory factors already work to “keep thousands of potentially harmful arthropod species permanently below economic thresholds,” and their central thesis, “Chemical control should act as a complement to the biological control.” They saw an opportunity where, with adequate understanding of the system, both methods could be made “to augment one another.” Perhaps most prescient was their statement that our failure to recognize the complex ecology inherent to pest management, “leads to the error of imposing insecticides on the ecosystem, rather than fitting them into it.” Of course, at the time, their idea about selective insecticides was in the context of a pest control system dominated by the broad-spectrum chlorinated hydrocarbon, DDT, and in the development of less persistent and less broad-spectrum organophosphate and carbamate alternatives.

Plimmer (1985) tied the term biorational to the process by which the control agent is designed and synthesized. He explained that biorational is “the exploitation of knowledge about plant or animal biochemistry in order to synthesize a new molecule designed to act at a particular site or to block a key step in a biochemical process.” However, this process-oriented definition fails to explicitly address selectivity towards a target or safety to non-target organisms. Bowers (2000) took this process approach one step further to incorporate the idea of selectivity by stating, “However, future needs clearly command the development of selective, pest-suppressive methodologies that rationally perturb those discrete aspects of pest biology and behavior that have arisen from the divergent evolutionary changes that separate invertebrate and microorganism from human biology.”

Definitions vary greatly, but others suggest that biorational agents should have limited or no affect on non-target organisms, including humans and their domestic plants and animals (i.e., least toxic, Diver and Hinman 2008). They are therefore generally narrower in spectrum, if not specific to phylum, class or even species of organisms. That being the case, the bio- prefix should not refer to source (as from a living system, or of ‘natural’ origin or makeup) so much as function (as compatible with living systems). Some define biorationals as biologicals or botanicals only. In this case, the former should be referred to as biocontrol agents and the latter may or may not be biorational depending on their degree of compatibility with living systems (e.g., rotenone or nicotine).

This limited or lack of adverse effects, while still controlling or suppressing the target pest, can be accomplished in any number of ways as outlined by Stern et al. (1959; *sensu* ‘selective insecticides’). One way in particular has placed otherwise potentially broad biocides into the rubric of biorationals. Those who view a lack of environmental persistence as a key attribute have labeled various salts, soaps and oils as biorational. It is true that many of these materials have direct contact action only and as such act on a population instantaneously with little to no residual effects. However, most agents of this kind are in fact broadly biocidal and thus can be used in a manner not compatible with living systems. Thus, the term biorational should be used descriptively as an adjective denoting compatibility with living systems within specific contexts. That is to say an insecticide may in fact be alternatively biorational in one system and decidedly not so in another [e.g., the insect growth regulator (IGR), pyriproxyfen, targeting a whitefly, *Bemisia tabaci*, in Arizona cotton (Ellsworth and Martinez-Carrillo 2001; Naranjo et al. 2003, 2004) as compared with the same compound used against scale insects in South African citrus (Hattingh 1996)]. Taken one step further, ecorational is another term used in many respects synonymously with biorational. Again, the compatibility of the control agent with the system in which it is used appears to be the governing principle (Ware and Whitacre 2004; Antwi et al. 2007). This context will be important in appreciating the scientific advances made in the pest control industry and described in this volume.

Finally, a discussion of the term biorational would not be complete without reviewing its first usage in the scientific literature by Carl Djerassi (Djerassi et al. 1974), a pioneer in the development of the first birth control pill. The term was introduced in this paper in order to avoid confusion between chemical and biological control of insects. Here again, biorational has seemed to occupy an important rhetorical space where the two approaches are compatible. Djerassi et al. (1974) gave examples of biorationals as pheromones, insect hormones, and hormone antagonists. While no definition was proposed, they noted that many biorationals are species-specific, often active at low concentrations, generally not persistent or toxic, and innocuous to vertebrates. It is true that the origins of this term suggest that the agents do not kill outright. However, Djerassi’s influence on the regulatory system of the time (US-EPA, which had only recently formed in 1970) likely led to this idea being captured and held by the term “biopesticide” as used today by the EPA (reviewed above). As a result, biorational has now come to include agents that either impact pest populations more subtly and indirectly as well as those that have

direct toxic action on their targets, but with great specificity. Either way, both Stern et al. (1959) and Djerassi et al. (1974) saw the importance of and greater need for education of the user of selective technologies (e.g., see Ellsworth and Martinez-Carrillo 2001).

Unfortunately, US-EPA has not clarified the issue of biorational pesticides. So they do not neatly fit within their regulatory framework. In 1997, the Food Quality and Protection Act brought forward new pesticide designations. “Reduced-risk” status is given to those candidate pesticides that do one or more of the following: reduce pesticide risks to human health, non-target organisms, or environmental resources, or help make IPM more effective (Uri 1998). Operationally, a biorational agent should be reduced-risk, but many potential reduced-risk pesticides may not be viewed as biorational. Without the weight of the US-EPA, it will be more difficult for a stable definition of biorational to gain traction in the literature. However, for this volume, we propose that the term be used in a bipartite manner to (1) describe substances or processes that when applied in a specific system or ecological context have little or no adverse consequence for the environment and non-target organisms, but (2) cause lethal or other suppressive or behavior modifying action on a target organism and augment the control system. Regardless of origin, these agents might be developed from natural or synthetic models, and generally exploit the evolutionary divergence of physiological systems in the target organism from non-target species including humans. If properly designed and deployed, a biorational agent should be nearly fully compatible with biological controls as envisioned for ‘selective insecticides’ by Stern et al. (1959) (also see Stansly et al. 1996).

3 Crop Protection Targeting Specific Biochemical Sites in Insect Pests

Various biochemical specific-sites of insects have been suggested as targets for developing pest control agents. By disrupting the activity of these sites, important processes could be affected resulting in pest mortality. Some examples of such methods using insect’s target sites have been summarized in other books (Ishaaya and Horowitz 1998; Ishaaya 2001; Horowitz and Ishaaya 2004). In this volume, we focus on specific targets such as insect neuropeptides, tyramine and octopamine receptors, GABA receptors, and on insect hormones such as ecdysone and juvenile hormones (analogs).

Insect neuropeptides have potential in the development of novel insecticides, because they are involved in many primary physiological and behavioral processes of insects (Gäde 1997; Altstein et al. 2000; Altstein and Hariton, Nachman – this volume). Insect neuropeptides are considered less toxic than small organic molecules and many of them are insect-specific. Two major limitations have delayed their use in pest management: (1) the linear nature of these peptides results in high susceptibility to proteolytic degradation and difficulties in penetrating biological tissues, and (2) it is difficult to design insect-neuropeptide antagonists because of their flexible 3D structures (Altstein et al. 2000). Altstein and Hariton (this volume)

summarize a strategy they have developed in their laboratory to overcome these limitations. The strategy, named INAI (Insect Neuropeptides Antagonist Insecticide), was applied to the insect PK/PBAN (Pyrokinin/Pheromone Biosynthesis Activating Neuropeptide) family. After they discovered a lead antagonist of PK/PBAN, they designed backbone cyclic (BBC) peptides that showed antagonistic activity; and thereafter, they improved the selectivity and stability of these antagonists. Following injection of these antagonists into *Helicoverpa peltigera* females, up to 70% inhibition of sex pheromone biosynthesis was achieved and treatment of *Spodoptera litoralis* larvae resulted in almost a full inhibition of cuticular melanization. These findings can be used for further development of other and more effective PK/PBAN antagonists-based insect control agents.

Another study (Hirashima, this volume) also suggests inhibiting pheromone production using agonists for the tyramine receptor. Arylaldehyde semicarbazones and 5-aryloxazoles highly inhibited *in vitro* pheromone production and calling behavior in the Indianmeal moth *Plodia interpunctella*. The author assumed that the targets of tyramine are the pheromone glands, resulting in a decline of PBAN concentration in the insect's haemolymph. Besides tyramine, other biogenic amines such as dopamine and octopamine, which widely exist in the central nervous system of insects (Evans 1980), might be involved in sex-pheromone production in connection with mating stimuli and mechanical stressors (Hirashima et al. 2007). However, the potential of these agonists in pest control are not yet achieved.

Gamma aminobutyric acid (GABA) is the major inhibitory neurotransmitter in both vertebrates' and invertebrates' central nervous systems (Roberts et al. 1976). GABA is released from the presynaptic neuron and moves across the synaptic cleft. It creates an electrical signal in the postsynaptic neuron by binding to its specific receptors. In their chapter on GABA receptors, Ozoe et al. (this volume) focus on the various GABA receptor ligands, their toxicity to insects and nematodes, their binding potencies and the effect of their agonists/antagonists on the receptors. Although GABA receptors have been considered an excellent source for developing specific insecticides, so far only two relatively new phenylpyrazole insecticides, fipronil and ethiprole (Caboni et al. 2003), have been discovered following the ban on use of organochlorine insecticides in use hitherto (dieldrin, and related organochlorine insecticides that are blocked the GABA-gated chloride channels were banned because of their persistence in the environment). However, a number of noncompetitive antagonists binding to GABA receptors and exhibiting insecticidal activity have been discovered. Similar to fipronil, they exhibited selectivity for insect vs. mammalian GABA receptors. This would enable the design of selective noncompetitive antagonists of GABA receptors, and due to the fact that they have ligand-multiple sites, various other sites could also be used to develop the third generation of safe and insect-specific insecticides targeting GABA receptors (Ozoe et al., this volume).

Ecdysteroids (20E) and juvenile hormones (JHs) regulate most of the physiological and biochemical processes during the insect's life cycle. Ecdysteroids affect and coordinate molting and metamorphosis processes, and JHs are responsible for the character of juvenile stages and for adult reproduction. Novel insecticides, which mimic 20E and JH action have been developed during the past three decades

(reviewed by Dhadialla et al. 1998) such as ecdysone agonists, JH analogs (JHAs) and JH mimics, e.g., methoprene, fenoxycarb and pyriproxyfen. In insects, metamorphosis is induced by ecdysteroid hormones in the absence of JHs. Therefore, persistence of JH or JHA during that time results in abnormal larvae or nymphs that are unable to develop to normal adults. Although some of the JHAs and JH mimics have been considered effective insecticides against various agricultural and medical pests, resistance to these agents, for example to pyriproxyfen in the whitefly *B. tabaci*, has developed a short time after its introduction into crop protection (Horowitz and Ishaaya 1994). The biological activities of JH have been well studied along with its molecular modes of action, especially in recent years. Palli (this volume) describes the genes and proteins involved in JH activity, mode of action of JH and JHA and their interaction with ecdysteroids. Finally he shows a model describing the possible molecular modes of action of JHs and JHA.

As an example, the gene '*Cfjhe*' (*Choristoneura fumiferana* [Spruce Budworm] Juvenile Hormone Esterase) is among those whose expression is regulated by both JH and 20E. This gene is induced by JH and its expression is suppressed by 20E. Expression of *Cfjhe* was found in four other insect species: *Trichoplusia ni*, *Heliothis virescens*, *Tribolium castaneum* and *Drosophila melanogaster* (Palli, this volume). Many other genes induced by JH were identified in *D. melanogaster*, which is an insect-model used for comprehensive study on molecular modes of action in insects (e.g. Dubrovsky et al. 2002; Li et al. 2007). A methoprene-tolerant gene (*met*) was also identified in this insect and this is the only example of target site resistance for JHAs (Wilson and Fabian 1986). Further research studies have shown the importance of *met* proteins in JH regulation along with its homologues in other insects, such as in *T. castaneum* (Parthasarathy et al. 2008).

Other studies suggested that JH and JHA, which antagonize 20E, are involved in specific processes in insects such as enhancing expression of immune protein genes, affecting programmed cell death of larval cells, and also connecting with the phosphorylation process. The proteins involved in their action interact and mediate cross talk between these hormones. Palli (this volume) concludes that although several proteins are significantly involved in JH signal transduction, the mechanism is unknown. Some possible modes of action were suggested, following the completion of whole genome sequencing. Available novel techniques make the insect *T. castaneum* an excellent model for further studies on JH action.

4 Exploitation of Plant Natural Products as a Source of Environmentally-Friendly Pesticides

Isman and Akhtar (2007) have reviewed various plant natural products with insecticidal activities. These natural substances are part of defensive chemistry that helps to defend plants from herbivores and pathogens. As they are naturally-occurring chemicals, the exploitation of such products may be useful for developing ecologically sound pesticides. Although there are several natural products that have been

developed as insecticides, there are numerous compounds that affect insects by interfering in their physiological processes. Azadirachtin (the major bioactive chemical in Neem) is an important natural product, which acts on insects in a manner similar to IGRs. However, to gain acceptable control one needs multiple applications. Its high cost and fast degradation render this product economically unfeasible (Isman 2004). Other products that have been reviewed (Isman and Akhtar 2007) are derivatives such as acetogenins from Annonaceae, alkaloids from Stemonaceae, naphthoquinones from the Scrophulariaceae, rocaglamides from Aglaia, and monoterpeneoids from plant essential oils. Although many compounds of plant origin have been found fully or partly effective as potential insecticides, Isman and Akhtar (2007) concluded that these natural compounds should be used as the starting point for the development of synthetic insecticides, as was done in the successful development of the pyrethroids from natural pyrethrins.

In this volume, Vandenborre et al. review the potential for insecticides based on plant lectins. Plant lectins are carbohydrate-binding proteins that are involved in plant defense and found in many plant species (Peumans and Van Damme 1995). Lectins incorporated in the diet or cloned in transgenic plants have shown some insecticidal activity to various insect orders (Van Damme 2008), especially Lepidoptera, Coleoptera, Diptera and Hemiptera. The main site of action for these compounds is the insect digestive system. The GNA- (*Galanthus nivalis*, the common snowdrop) related family is one of the major families that have been tested. An unclear point with regard to lectins is their impact on beneficial arthropods such as parasitoids, predators and pollinators. Many research studies, which incorporated lectins either in diets or in transgenic plants, have shown that low (and even high) doses of GNA had no effect on beneficial insects. However, others did show adverse effects on bumblebees, solitary bees and lady beetles, and also on some parasitoids, especially at high doses (Birch et al. 1999; Romeis et al. 2003; Babendreier et al. 2007). Vandenborre et al. (this volume) concluded that although the lectins apparently have minor impact on beneficial insects there is still a great potential to exploit them as expressed in transgenic plants, especially targeting hemipteran pests, which are insensitive towards Bt-transgenic crops.

5 Utilization of Semiochemicals (Pheromones) and Other Insect Communication Signals for Controlling Insect Pests

El-Sayed (2008) defined pheromones and semiochemicals as "...signaling chemicals that organisms can detect in its environment, which may modify its behavior or its physiology". Semiochemicals are considered safe and environmentally friendly substances because they are natural, generally volatile chemicals and are specific to the target insect without leaving any residues. The term pheromone was suggested by Karlson and Lüscher in a letter to "Nature" (1959). They wrote: "...various active substances which, though they resemble hormones in some respects,

cannot be included among them...Unlike hormones, however, the substance is not secreted into the blood but outside the body... (and it serves as) communication between individuals". Since then, pheromone identification has triggered their use in pest control. However, difficulties in practical application resulted in some loss of interest in their use. Cokl and Millar (this volume), in their comprehensive review on utilization of insect signaling for monitoring and controlling of insect pests, believe that these signals should be exploited for insect-pest management. In their chapter, they focus on two types of insect signals, chemical and mechanical. The chemical signal includes mainly sex pheromones, which mediate behavioral communication between the sexes, and aggregation pheromones that are produced to attract conspecific individuals to a host resource (a host tree – as is found in various bark beetles) or attract both sexes for reproduction. Other types of pheromones are used as alarm, trail (especially in social insects), and marking (territory or host).

5.1 Ways for Exploiting Pheromones

Pheromones have been exploited in several ways:

1. Monitoring of insect populations using “pheromone traps” for species such as the gypsy moth, the boll weevil, the pink bollworm (PBW) and the med fly. In general, sex pheromones that attract insect males have been used as a practical monitoring tool for early detection of local or invasive pests (Cokl and Millar, this volume).
2. Mating disruption is a common and successful use of sex pheromone technology (reviewed by Cardé 2007). The idea is to saturate an area-wide crop with synthetic insect pheromone, which interferes with the sexual communication of a specific insect pest. Among the main target pests have been the gypsy moth, codling moth, grapevine moths and pink bollworm. The mating disruption method was an important IPM tactic for controlling the pink bollworm in the Southwest of the USA before the era of Bt-cotton, after which its use has been reduced dramatically. A new eradication effort to control this pest was the use of the mating disruption method in conjunction with other strategies: (a) extensive survey; (b) transgenic Bt cotton; (c) pheromone application for mating disruption; and, (d) sterile PBW moth releases. Adoption of Bt cotton in Arizona exceeds 98% of cotton acres, with mating disruption concentrated on the remaining 2% of the area. So far, this eradication action seems to be highly successful (Grefenstette et al. 2008).
3. Mass trapping of insect pests is technically feasible but its cost and the extensive labor required has limited its use. However, pheromone-based mass trapping is still a major component of IPM programs for tropical fruits in many tropical and subtropical regions (Cokl and Millar, this volume).
4. “Attract and kill”, a method combining the use of pheromone as attractant and an insecticide as a toxicant, is an effective method to control the pink bollworm, the codling moth, fruit flies and the boll weevil (Butler and Las 1983; Lösel et al. 2000; Bostanian and Racette 2001; Spurgeon 2001).

Mealybugs are pests of worldwide importance that could potentially be managed through pheromone and other environmentally friendly technologies as suggested by Franco et al. (this volume). Mealybugs are severe sap-sucking pests attacking many agricultural crops such as citrus, apple, vineyards, persimmon and other subtropical fruit trees, coffee and fresh herbs. After extensively reviewing the biological characteristics of mealybugs, their host plants and natural enemies, these authors propose reducing mealybug males to prevent mating during periods when they are at low level. In practice, one can use mating disruption; however, there are still some difficulties in synthesizing mealybug sex pheromones. For example, the synthesis and therefore use of the *Planococcus citri* homolog is easier and cheaper than the pheromone (A. Zada et al. unpublished data, 2008). ‘Attract and kill’ using pheromone baits and contact poisons was mentioned as an additional means to annihilate mealybug males. This approach should be accompanied by other tactics such as monitoring, detecting and chemically treating mealybug hotspots and detection and augmentation of natural enemies (Franco et al., this volume).

5.2 *Insect’s Mechanical Signals*

Cokl and Millar (this volume) describe a possible exploitation of mechanical signals in controlling insect pest. These signals are used by arthropods for communication and can be defined as contact (tactile) signals, airborne sound, waterborne sound or substrate-borne sound. Their model for sound communication is the stink bug, *Nezara viridula*. Polajnar and Cokl (2008) have shown that it is feasible to disrupt the vibrational sexual communication in stink bugs by using artificial signals. These experiments need to be verified under field conditions, with the major obstacle of this method being how to vibrate large numbers of plants outdoors. Notwithstanding, the use of such artificial signals to disrupt acoustic communication is intriguing.

6 **Biotechnology Manipulations (Genetic Approach) as Novel Strategies Against Arthropod Pests**

The application of biotechnology for crop protection commenced on a large scale in 1996, and had increased 67-fold by 2007, reaching more than 114 million hectares worldwide; making it the fastest adopted crop technology in recent history (James 2008).

In 1987, Vaeck et al. published their classic article regarding transgenic tobacco plants expressing genes of Bt, which protect them from insect damage. Since then, Bt crops have become a great success of applied biotechnology in agriculture, especially to control lepidopteron pests in cotton and maize. So far, most of the genetically modified crops, which exhibit insecticidal activity, consist mainly of

the toxin CryIAc in transgenic cotton and CryIAb in transgenic corn (Tabashnik and Carriere 2009). In 1996, Bt crops were first commercially planted reaching 42 million hectares during 2007, and this technology has reduced substantially pesticide applications (Brookes and Barfoot 2008; James 2008).

As not all pests are susceptible to Bt toxins (e.g. sucking pests and stored product pests) solutions other than Bt should be developed, such as plant defensive proteins (see Vandenborre et al., this volume), secondary metabolic compounds and RNA interference (RNAi) (Gatehouse 2008).

In this volume, Alphey et al. have reviewed recent advances in biotechnology for crop protection and insect suppression. These include the use of transgenic insects with conditional lethal genes, symbiotic control of insect pests and disease vectors, and other use of symbionts for controlling pest populations (see also Darby, this volume).

A potential pest suppression approach involves modification of insects by engineering conditional lethal genes. This method is intended to replace irradiation as it is currently used for SIT (sterile insect technique). The lethal gene accumulates in a population and, over several generations, causes a decrease in population size (Alphey 2007). In support of the PBW eradication program that is underway in the Southwestern USA, an engineered strain of PBW was developed with a dominant lethal mutation (RIDL; though not yet implemented for PBW control). ‘Genetic sterilization’ of progeny results from the mating of wild types with RIDL insects, eventually leading to widespread pest suppression. Release of this strain under laboratory conditions resulted in 60% to 92% larval mortality. This method can be used for replacing the radiation-based sterilization process or as a supplement to the classic SIT (Simmons et al. 2007). RIDL technology also has been successfully introduced into other major pest species (Alphey et al. this volume).

Other advances in biotechnology of insects provide a new strategy for controlling insect borne pathogen transmission of human diseases and also vectors of plant pathogens. One application of this strategy that was tested in mosquitoes under laboratory conditions is the modification of genes that suppress pathogens’ development (e.g., *Plasmodium* sp.) (Alphey et al. 2002; Abraham et al. 2007). One problem is how to efficiently spread these genes (the ‘effector’ or ‘refractory’ genes) in the field by an additional gene-driven system. Although there are considerable technical and regulatory problems to using this strategy, it has the potential to be very promising with major positive health consequences for the human population (Alphey et al. this volume).

A similar strategy is “paratransgenesis” or symbiotic control, also studied in mosquito-borne pathogen systems. Paratransgenesis is a genetic manipulation of the insect’s symbiotic bacteria. The idea is to alter the disease vector’s ability to transmit a pathogen (Beard et al. 2002; Riehle et al. 2003; Miller et al. 2007; Ren et al. 2008). One critical step to success with this strategy is to select an appropriate candidate symbiont, a major stumbling block for this research (Ren et al. 2008). Symbiotic control is a biologically-based method and may be the least disruptive to the ecosystem. However, it is still subject to severe regulatory inspection (Miller et al. 2007). This strategy has been adopted for controlling the Pierce’s disease – a serious disease of grapevines (Miller et al. 2007). In this study the researchers

manipulated the symbiont *Alcaligenes xylooxidans* var. *denitrificans* that occupies the same niche at the pathogen, *Xylella fastidiosa*, causing Pierce's disease is transmitted by the glassy-winged sharpshooter (*Homalodisca vitripennis*).

The bacterium, *Wolbachia pipientis* ('Wolbachia') is a widespread and abundant secondary cytoplasmic-symbiont of arthropods and nematodes (Stouthamer et al. 1999). *Wolbachia* spp. are involved to a great extent in manipulation of its host's reproductive properties including the induction of parthenogenesis, feminization, male killing and cytoplasmic incompatibility (CI). CI most associated with *Wolbachia* infection is a biological phenomenon causing a decrease in population numbers of those not carrying the specific cytoplasmic factors. There are many suggested ways that *Wolbachia* can be used to control insect pests (e.g. Ioannidis and Bourtzis 2007; Alphey et al. this volume). For example, *Wolbachia*-induced CI has been used for population suppression of the medfly, *Ceratitidis capitata* (Zabalou et al. 2004). This technique is similar to SIT and is termed 'IIT' ("Incompatible Insect Technique"). In IIT, the males released into the field are infected with a *Wolbachia* strain and the target population is either uninfected or infected with an incompatible strain, hence, it results in a target-population decrease. Another suggested application is to spread desired genotypes in pest populations by using the driving ability of the CI phenotype (Ioannidis and Bourtzis 2007); in the same way, the virulent strain of *Wolbachia* can modify age structure of disease-borne vector populations resulting in suppression of disease transmission (see also Alphey et al., and Darby this volume).

All the above illustrate the importance of symbiotic control and its potential in pest and disease management.

7 Pesticide Resistance and Management Strategies

Pesticide resistance in arthropod pests, insects and mites, is a seriously increasing phenomenon in crop protection. Based on the Arthropod Pesticide Resistance Database (APRD), more than 550 species of arthropods have developed resistance to pesticides (Whalon et al. 2008). Pesticide resistance causes the disuse of effective pesticides and diminishes the pesticide diversity that is one of the basic principles in pest resistance management.

Managing resistance requires a practical solution to problems resulting from the adaptability of the insect pests to the used insecticides. In general, pests most prone to developing resistance are those with primary targets of numerous insecticide treatments, because they often are most abundant and damaging (Denholm et al. 1998). The whitefly, *B. tabaci*, and the two-spotted spider mite, *Tetranychus urticae* exemplify this phenomenon of rapid evolution of pesticide resistance. Through their resistances, these pests cause a decline in the number of effective pesticides and place new insecticides under severe threat of overuse.

Insecticide resistance management (IRM) is an important part of any IPM program in crops where pesticides are used frequently (Wise and Whalon, this

volume). The main purposes of IRM are: rational use of pesticides, reducing the number of treatments, combating resistance to available and effective insecticides, prolonging the life span of new insecticides by optimizing their use, and preserving natural enemies (Horowitz et al. 1995); all of the above goals are in high accordance with most IPM programs, though compatibility should not always be assumed (e.g., see Crowder et al. 2008).

Resistance management is based in resistance prevention, a positive outcome for IPM; however, resistance management goals are not always entirely consistent with IPM goals. The two concepts can ostensibly be at odds. IPM depends on pest prevention and maintenance of pest levels below economic levels. Resistance management, on the other hand, depends on a certain abundance and mobility of susceptible insects in a system. Occasionally, the densities of pests needed to secure resistance management are above economic thresholds established under IPM. Or, the assumptions for insect movement by resistance management models (to facilitate mating of susceptible and resistant individuals) are counter to tactics of isolation or strategic crop placement implemented for IPM. In another example, resistance models that optimize resistance evolution towards one technology by limiting its use place greater resistance pressure on other classes of chemistry, which are used alternatively and potentially multiple times. When this occurs, growers may fail to reach the economic goals stipulated by their IPM program. Few resistance studies have attempted to reconcile these issues; however, feedback of risks for future resistances should be incorporated into the IPM framework, most likely through adjusted economic thresholds (e.g. Caprio 1998; Hurley et al. 2002; Onstad et al. 2003; Crowder et al. 2006, 2008).

Knowledge of the target pest's biological characteristics, and the genetics and mechanisms of pesticide resistance in the pest is essential in pest resistance management programs. However, despite our rapidly increasing knowledge of the biochemical and molecular nature of resistance, it seems that management strategies still rely largely on common sense and practical tactics even though different resistance mechanisms may be present (Horowitz and Denholm 2001). Common sense is grounded in practical resistance management truisms: (1) *limit insecticide use to the lowest practical level*; (2) *diversify insecticide use patterns*; and (3) *partition insecticides among crops and pests such that modes of action are segregated as much as is practically possible* (e.g., see Ellsworth and Diehl 1998).

Van Leeuwen et al. (this volume) thoroughly reviewed the extent and mechanisms of resistance in the two-spotted mite, *T. urticae*, one of the most serious pests of glasshouses worldwide. Although biological control of *T. urticae* using predatory phytoseiid mites has been implemented with success, chemical control by acaricide applications is still essential in both glasshouses and outdoors. This pest is extremely prone to developing rapid resistance and cross-resistance to many acaricides that have been used against it; however, in depth studies on mechanisms of acaricide resistance are scanty.

Resistance to OPs, the first chemical group used to control *T. urticae*, has occurred a short time after their introduction in the USA and Europe, with the main mechanism being reduced sensitivity of the enzyme acetylcholinesterase (AChE).

Resistance in this pest to pyrethroids, another important group of insecticides, is also widespread and the suggested main resistance mechanisms are metabolic, either enzymatic hydrolysis by carboxylesterases or oxidation by microsomal monooxygenases (e.g. Van Leeuwen et al. 2007). The pyrethroid target site is the voltage-gated sodium channel in nerve cells. Target site insensitivity to bifenthrin (a pyrethroid that has been used often against *T. urticae*) has been investigated at the molecular level (A. Tsagkarakou et al., unpublished data, 2009) and this study proved that target site insensitivity in *T. urticae* is also involved in resistance to pyrethroids.

Since the 1990s, a group of acaricides with similar modes of action have been introduced and classified as mitochondrial electron transport inhibitors (METI), inhibiting complex I of the respiratory chain (e.g. Hollingworth et al. 1994). Resistance to the METI group in *T. urticae* has been detected since the mid 1990s, and cross-resistance among different acaricides of this group has been observed worldwide (Van Leeuwen et al., this volume). The mechanisms of resistance to METI pesticides include mainly oxidative detoxification (metabolic). Based on molecular studies, it is also suggested that single point mutations that affect the binding of METI acaricides to complex I cause target site resistance in *T. urticae* (Van Pottelberge et al. 2008).

An interesting approach to integrated pest and resistance management in tree fruit orchards is described by Wise and Whalon (this volume). Following the introduction of new insecticides that replaced the conventional broad spectrum insecticides, they posit that a total switch to the new insecticides and abandoning the conventional ones is risky and can result in field control failures. Hence, they recommend a return to a ‘system approach’ in IPM “...to meet the demands of global markets, economics, and human and environmental safety expectations”.

The first task in a system approach is to define its components such as crop area, pests and beneficial-insect populations, and the production factors of the growers. The next step is to clarify the interactions between each component. The authors demonstrated their system approach through a simple model called the ‘PIC (Plant-Insect-Chemical) Triad’, and noted that we must consider all the inherent interactions to create a powerful data-based system designed to optimize insecticide performance and other components relevant to IPM. When new insecticides are introduced, significant ecosystem impacts may occur, because the whole pest complex is generally not controlled. Thus, the loss of broad spectrum insecticides engenders the introduction of several new insecticides. In their field experiments, Wise and Whalon (this volume) examined the levels of natural enemies in cherry orchards, in contrasted regimes of conventional and new insecticides. Surprisingly, beneficial levels are significantly reduced following applications of new insecticides (“reduced risk”). Notwithstanding, their finding is in contrast with other research studies that were conducted in various cotton fields (e.g. Naranjo et al. 2003, 2004; Mansfield et al. 2006). Wise and Whalon (this volume) conclude that the effect of both types of insecticides should be examined under field conditions with a consideration of the whole ecosystem. Here again, determination of a biorational pest control approach is system-specific and context-sensitive. A broad-based IPM

program (including IRM) should use suitable monitoring tools to identify the contribution of natural enemies as they play an important role in pest and resistance management, in addition to the study on the impact of the insecticides used on mortality and resistance in key pests (*sensu* ‘biorational’ and life table analyses; Ellsworth and Martinez-Carrillo 2001; Naranjo 2001; Naranjo and Ellsworth 2005).

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