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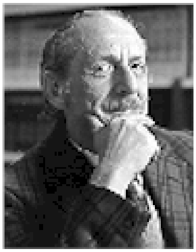

Current Comments®

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The Cockroach Connection—Ancient, Seemingly Indestructible Pest. Part 2. Population Control, or: "Dr. Djerassi, How Do You Get Them to Take the Pill?"

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In Part 1, we examined the cockroach's morphology and behavior and the link to allergic reactions in humans. In Part 2, we examine how scientists are attacking the problem of cockroach infestations via pesticides and artificial analogs of the insect's hormones and pheromones. Four *Citation Classics*® relating to research on cockroach development and growth are discussed, and ISI® research-front data highlight activity in cockroach control.

Declaring War on Roaches

The cockroach is one of the most vilified insects known to man. In the US more than $1.5 billion was spent in 1989 on consumer pesticide products to get rid of cockroaches, the single largest expenditure for a pest in the country.[1] Let's take a look at what this money is spent on and at the eradication/control efforts of insect researchers in the laboratory.

Scientists are attacking the problem of cockroach infestations in three ways: by using chemicals that attack the roach's central nervous system, by using those that mimic the insect's hormone/endocrine system (causing disruptions in the life cycle), and by using artificially synthesized pheromonal attractants to draw cockroaches to sex-bait traps where they get stuck in a glue and die.

Chemical Pesticides

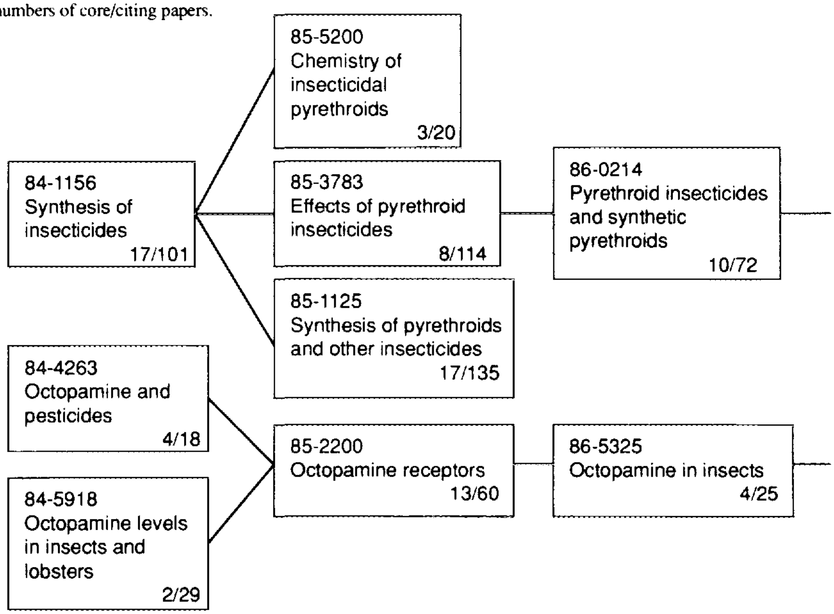
One of the oldest insecticides known to man is pyrethrum. Pyrethrin insecticides are derived from pyrethrum flowers, such as chrysanthemums. The aromatic flower heads are powdered or extracted with solvents, and the resultant substances are contact poisons and nerve toxins for insects.[2] Because natural pyrethrins are unstable and expensive, chemists have produced synthetic pyrethroids that mimic the natural pyrethrins. These are more stable and break down less easily. Many of the pyrethroids are much more active than the natural pyrethrins (some 1,000 times more) and, unlike the natural pyrethrins, are stable in sunlight. In contrast, because of their instability in sunlight, the natural pyrethrins cannot be used on field crops. Permethrin was the first sunlight-stable commercial pyrethroid.[3]

Many insects have developed a resistance to pyrethrins and pyrethroids (synthetic derivatives of pyrethrins). According to Clive A. Henrick, Sandoz Crop Protection Research Division, Palo Alto, California, general insect resistance is becoming widespread,[3] with the cockroach fast becoming one of the insects that is resistant.[4] Considering that each generation of roaches follows itself in quick succession (survivors passing on their resistance to offspring), this comes as no surprise.

The organophosphates constitute another category of insecticides used on roaches. These include chemicals called chlorpyriphox, malathion, diazinon, and dichlorvos (also known as DDVP). These chemicals work by inhibiting the enzyme cholinesterase. This causes nerves to stimulate muscles continuously. Some organophosphates are fairly toxic to mammals, while others, including malathion, are of low toxicity and break down rapidly.[5]

The carbamates, including bendiocarb and propoxur, encompass another category of roach insecticide. Carbamates are used most frequently in over-the-counter sprays

Figure 1: Historiographs of research fronts on chemical insecticides. Numbers at the bottom of each box indicate numbers of core/citing papers.



and professional applications because they act within minutes—one of the quickest acting contact poisons. These have the same mode of action as the organophosphates.

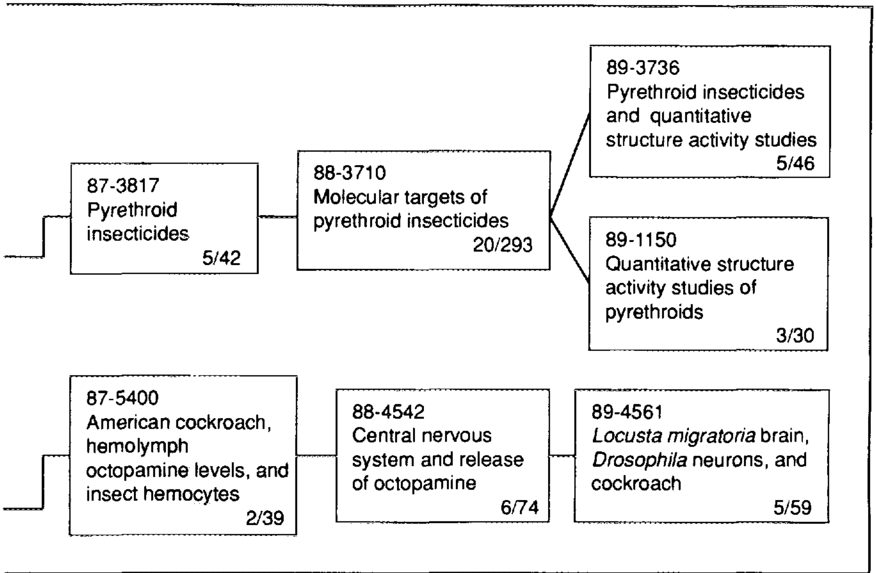
Another chemical group is composed of inorganic dusts. These include silica gel and boric acid. These are called "mechanical" insecticides because they kill the roaches by dehydration. Boric acid also works as a stomach poison, but is toxic to pets and humans.[5] The inorganic dusts lose their effectiveness in humid weather. But when combined with pyrethrins, they are used as an agent to flush cockroaches from their hiding places.

The number of chemicals, however, that cockroaches are becoming resistant to is growing. In one recently published study of insecticides and their effects on the German cockroach, S.J. Barcay and colleagues, Purdue University, West Lafayette, Indiana, found that pyrethrins, diazinon, permethrin, and propoxur in lethal quantities "did not induce any signficant changes in cockroach distribution." With sublethal doses, the roaches "settled to their original distribution 24 hours after treatment." Results from both experiments indicate that thorough insecticide applications "do not significantly affect German cockroach population dispersal or movement patterns within apartments."[4]

Another recent study looked at the performance of consumer roach bait products. It found that, of all those available, hydramethylnon (the active ingredient in Combat roach traps) "has the greatest potential for field effectiveness. Only hydramethylnon significantly reduced German cockroach populations."[6] Hydramethylnon is a chemical that affects the cell's ability to convert food into energy. The net result is that the insect eats the chemical, slowly runs out of energy, falls asleep, and dies.[7]

Repellents: Shoo, Roach, Don't Bother Me!

I don't think that anyone would argue that we'd prefer cockroaches to stay outdoors. As for ways of making these insects leave (instead of exterminating them), there have been numerous suggestions, ranging from old home remedies, such as cucumbers and bay leaves,[8] to highly touted high-tech



ware, such as ultrasound. The high-pitched noise, according to proponents, drives away all sorts of insect pests, including cockroaches. Unfortunately, studies show that German cockroaches enter "ultrasound-treated rooms as readily as they [do] untreated rooms."[9]

On the biochemical front, scientists report that synthetic and naturally occurring chemicals both have repellent properties, according to controlled studies on the German and the American cockroach. The synthetic chemicals include amides, sulfonamides, carboxamides, and cyanoacetic acids. Naturally occurring chemicals include plant oils from the Japanese mint and Scotch spearmint.[10] Usually, these repellents are used in concert with insecticides to achieve the greatest deterrent effect.

There may be a better, nonchemical solution to the cockroach infestation problem, however—build better houses! At the US Department of Agriculture laboratory in Gainesville, Florida, entomologists are monitoring cockroach activity in a specially built attic in an effort to understand what factors control cockroach movement.[11] In this building 100 sensors and probes set at various locations measure humidity, temperatures inside insulation and wood, airflow patterns, as well as roach distribution and activity (via proximity sensors and video).

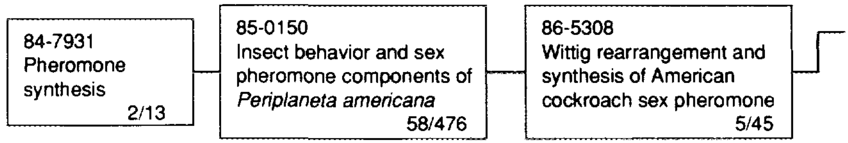
Gainesville scientists hope to determine what conditions the insects need to thrive—whether in the attic, among the insulation, or in the walls. From these data, it may become possible through new home construction techniques to repel cockroaches. To date, scientists have found that roaches thrive in areas of stagnant air and high humidity, and that they avoid dry, ventilated environments.

Cockroach Biochemistry and *Citation Classics*® : Putting Roaches on the Pill

In addition to synthetic and naturally occurring pesticides, scientists seek to control cockroaches through the insect's own biochemical reactions. Studying these reactions helps insect researchers understand how cockroaches mature from egg to nymph to adult. The studies also provide hints as to where artificial mimics of the hormone regulators of these reactions might be used to disrupt the cockroach's developmental and behavioral processes.

The road to manipulating the cockroach's biological processes actually began nearly 40 years ago, when entomologists discovered that a series of proteins which affect egg yolk production in vertebrates also appeared in insects.[12] In the following decades, studies on how these proteins affect

Figure 2: Historiograph of research fronts on cockroach sex pheromones. Numbers at the bottom of each box indicate numbers of core/citing papers.



egg production and insect nymph growth led to efforts to identify and manipulate insect hormones. Many of the discoveries dealing with these insect hormones took place in the late 1960s and 1970s.[13-15]

The Discovery of Insect Vitellogenins

We have four *Citation Classics* that follow the development of this interesting branch of entomology.[12-15] Although they are not specifically on cockroaches, the commentaries are generally applicable. They begin in 1951 with the discovery of the egg yolk proteins called vitellogenins, then move to establishing the connection of hormones in regulating these proteins, and finally to the branching out of studies in the regulation of the hormones that affect insect molting and metamorphosis through the varying stages from egg to nymph to adult. These hormones include brain hormones (called peptides), molting hormones (called ecdysones), and juvenile hormones, which modify the outcome of the molt.

Vitellogenin is the generic name for a group of proteins synthesized outside the ovaries that become the major egg yolk vitellin. This protein is manufactured in both vertebrates and insects. Vitellogenesis in many insects, the cockroach included, depends on the secretion of juvenile hormones from the corpus allatum, a part of the roach endocrine system that regulates juvenile characteristics in the larva and is responsible for oocyte (egg case) development and secondary sexual organ secretion in the adult roach.[16] However, the main function of insect juvenile hormones is to control the outcome of each molt (it maintains the immature character of the developing insect) while their secondary functions are involved with yolk formation.[3]

In his 1979 commentary[17] on the 1951 vitellogenin discovery and resulting review paper,[12] W.H. Telfer, University of Pennsylvania, Philadelphia, noted that vitellogenesis studies came into their own during the mid-1960s with the discovery of the organelle for vitellogenin transport, as well as when the endocrinological community concentrated their efforts on this field.

The Vitellogenin/Ecdysone Hormone Connection

While vitellogenesis was discovered in the early 1950s, it wasn't until the 1970s that vitellogenesis in other insects was linked to steroid hormones generated by the gonads. In his *Classic* commentary[18] on the landmark paper[13] that was the first to report that ecdysone (a molting hormone) stimulated vitellogenin synthesis in the fat body of the mosquito, Henry H. Hagedorn, University of Arizona, Tucson, comments that "by 1975 very little was known about the hormonal control of egg development, except for the common observation that removal of the source of juvenile hormone[s] somehow interfered with the process.... Since, for the most part, insects chosen for physiological work are large, it is noteworthy that work on the tiny mosquito opened new doors in this field." Ecdysone was first identified in 1956 in Germany by biochemist Peter Karlson, University of Munich, and colleagues who started with 1,000 pounds of silkworm pupae to extract the small amounts of the chemical that were harbored by each insect.[19]

Another *Classic* paper also concerns the hormone ecdysone and its effect on molting of the embryo in the locust.[14] According to their *Classic* commentary, M. Lagueux, M. Hirn, and J. A. Hoffmann, Louis Pasteur

87-5389 Synthesizing vinblastine derivatives and Wittig rearrangement 3/34	88-208 Diurnal rhythm of *Blatella germanica* L. and American cockroach 6/39	89-2268 Wittig rearrangement, allylic ethers, and American cockroach 8/62

University, Strasbourg, France, found serendipitously that ecdysone not only stimulated molting and metamorphosis in adult insects, but also regulated molts of the developing embryo. They were originally trying to prove that ecdysone was only a molting hormone and believed that adult female locusts would prove this since they would no longer undergo further growth. Each molt of the embryo was preceded by or coincident with a concentration peak of the ecdysone hormone. Their observations "probably represent the best documented example of a transfer of steroid hormones of maternal origin to the embryo in egg-laying animals."[20]

Early Work on Juvenile Hormones

While vitellogenesis and hormone regulation were not linked until the 1970s, the first paper on the identification of an insect juvenile hormone was published in 1967.[21] Prior to this, the chemical structures of natural juvenile hormones were unknown (although the presence of juvenile hormones was established in the 1930s[3]).

The potential to selectively control insect pests by using analogs of their natural juvenile hormones was realized in late 1970 at a start-up company named Zoecon Corporation, Palo Alto. The compound, called hydroprene, was the first juvenile hormone mimic synthesized that eventually became a commercial product (it was actually the 394th mimic synthesized[5]), with a second appearing in 1971 called methoprene. These chemical compounds, based on ethyl and isopropyl esters, are potent hormone mimics that cause some insect species that come into contact with them to be irreversibly sterilized. A paper describing these compounds and their effects was published subsequently in 1973.[15]

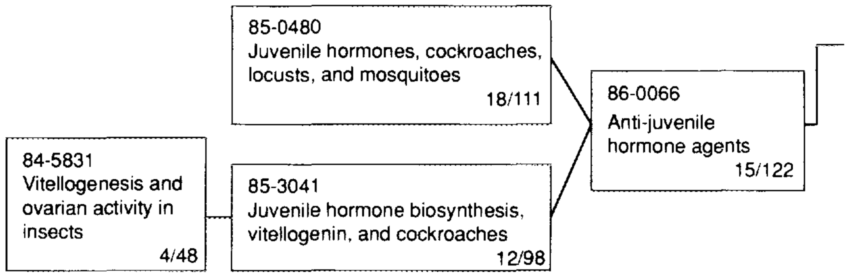
In his *Classic* commentary on the development of juvenile hormone mimics at Zoecon Corporation, Henrick gives a thumbnail sketch of methoprene:

> Methoprene became our first commercial product, and it has been used worldwide as the standard [juvenile hormone mimic] since its discovery.... Methoprene was the first "biorational" insecticide, a term coined...in 1974[22] to describe our approach to developing new environmentally safe pesticides. Methoprene is remarkably nontoxic to mammals.... It is in a sense also nontoxic to young insects in that it has no effect on early larval [stages] and only affects the last larval stages by interfering with metamorphosis.... The commercial success of methoprene and subsequently hydroprene (for cockroach control) has fully justified the initial enthusiasm and marked the beginning of the use of biorational insecticides.[23]

Hydroprene has been shown in field-test situations to reduce cockroach populations by 95 percent within six months after an application of the compound.[5] Speaking of hormone regulators for cockroaches, Carl Djerassi, Stanford University, California, has been (over the years) involved in this quest. Back in the mid-1980s, when he also served as chief executive officer of Zoecon Corporation (a company specializing in the development of insect biochemical regulators), Carl publicized a cockroach sterilizer called GENCOR, which contains hydroprene as the active ingredient. In a forthcoming autobiography, Carl recalls his advertising experiences:

> I premiered on the cockroach circuit in Orlando, Florida, where newspapers were at the time full of stories of sightings of the Asian cockroach.... I did TV interviews on the same day in four local stations: the mother of Zoecon's newest

Figure 3: Historiograph of research fronts on insect juvenile hormones. Numbers at the bottom of each box indicate numbers of core/citing papers.



> president, John Diekman, was astonished to see her son's former professor pontificating about cockroaches on her favorite Orlando channel one afternoon, then again on the new channel she switched to, then again on the evening news of a third channel! My professorial spiel started with my early work in the 1950s on steroid oral contraceptives, then noted the conceptual similarity between Zoecon's research and the development of the Pill, and ended by calling GENCOR a fundamentally new prophylactic approach to cockroaches. My references to "cockroach birth control" may have been too clever for our own good or perhaps I was catering too much to the anthropomorphism of my TV hostesses, because invariably I would hear some version of "But doctor, how do you get a cockroach to take the pill?" My explanation that one had only to spray room corners, baseboards, and other likely paths seemed to disappoint them.[24]

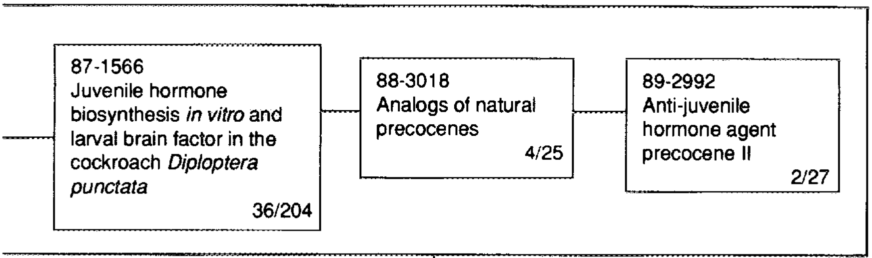
Juvenile hormones are only one type of insect biochemical that entomologists, organic biochemists, and endocrinologists are researching. Another family of these biochemicals are the pheromones.

Pheromonal Lures: The Cockroach Honey Trap

In an effort to have a mechanism to control infestations, insect researchers have been active for more than 25 years in trying to isolate, characterize, and synthesize the female cockroach sex pheromone. Many insects, the cockroach included, use various pheromones to mark territorial boundaries, pathways to food sources (one of the reasons Roach Motel traps work), and, of course, to attract members of the opposite gender.

The sex pheromones released by females biologically communicate to males of their species that they are in a sexually receptive condition. Some insects, like moths, can detect from miles away the pheromone given off by a receptive female. It should be stressed, however, that many natural pheromones are short-lived and need to be continuously produced to be useful over long periods of time.[25,26] In cockroaches there are a number of pheromones (such as wing-raising sex pheromones, "arrestant" male pheromones for keeping the female quiescent during mating, and aggregation pheromones to bring other roaches to a specific area), but for the most part these are effective over very short distances, such as three inches or less.[27]

The first successful synthesizing of the sex pheromone of a cockroach species happened in 1974. C.J. Persoons, F.J. Ritter, and W.J. Lichtendonk, TNO, Delft, The Netherlands, identified four biologically active components of the sex pheromone of the American cockroach.[28] The Dutch scientists isolated two of these chemicals, which were called periplanone-A and periplanone-B. This group was elemental in identifying the structure of periplanone-B and the subsequent artificial synthesis of this chemical in 1979.[29] H. Hauptmann, G. Mühlbauer, and H. Sass, Regensberg



University, Germany, were the first in 1986 to successfully synthesize a version of periplanone-A.[30]

Entomologists have learned that the use of pheromones can affect the cockroach's diurnal rhythm (the habit of avoiding light and concentrating activity—such as foraging and sexual behavior—in the dark and at night) and that male roaches will follow the pheromone scent almost anywhere.[31] This latter finding forms the basis of some of the popular roach traps, in which a periplanone-B/glue mixture awaits amorous male roaches that get stuck in the glue and either die of starvation or of contact poisons lacing the glue. However, it should be noted that periplanone-B is mostly an excitant chemical for males and not an attractant. According to Henrick, "It only works on the American cockroach (10 percent of the US problem) and *not* on the German cockroach (about 80 percent of the problem)."[3]

ISI® Research Fronts Highlight Activity on Insecticide, Pheromone, and Juvenile Hormone Investigations

Figures 1, 2, and 3 illustrate, via historiographs, research on cockroaches during the years 1984 through 1989. A research front is formed by the connections made by scientists in their referencing patterns. Using a method called co-citation clustering, it is possible to order automatically the scientific literature into bibliographically distinct and intellectually coherent units. Articles that are frequently cited together by current papers constitute the "core" of the specialty. The research front, in part, is composed of citing articles and is named from phrases co-occurring in these citing titles. If core papers are co-cited during a number of consecutive years, the research fronts are linked.

Pesticides

Figure 1 represents two distinct series of linked research. Both highlight studies of cockroach central nervous system functions with the effects of nerve toxins. The upper series of research specialties focus nearly exclusively on pyrethroid insecticides. Two of the fronts, #87-3817, "Pyrethroid insecticides," and #88-3710, "Molecular targets of pyrethroid insecticides," indicate a significant upturn in this field of research. The number of core papers increased fourfold (from 5 in 1987 to 20 in 1988), and the number of citing articles increased nearly sevenfold (from 42 to more than 290).

The lower series of fronts emphasize research in identifying neural transmission mechanisms and of a chemical found in cockroaches called octopamine. Octopamine is a neurotransmitter found in the hemolymph (body fluid or blood) of the insect. Hemolymph circulates through the fat body, the main organ of intermediary metabolism that also stores protein during metamorphosis.[32] If octopamine release is inhibited or interrupted, the cockroach's ability to eat, grow, and reproduce is severely affected, if not stopped outright. The research-front titles indicate that octopamine research is closely linked to hemolymph cell studies and central nervous system experiments. Octopamine agonists (chemical substances that combine with a nerve receptor and initiate a reaction) are aimed at affecting insect behavior by exciting the central nervous system.[3]

Sex Pheromone Studies

Figure 2 emphasizes work on synthesizing cockroach pheromones. Two of the research fronts, #84-7931, "Pheromone synthesis" and #85-0150, "Insect behavior and sex pheromone components of *Periplaneta americana*," indicate a research explosion in this field of entomological biochemistry. The number of core papers during the two years increased nearly 30-fold, and the number of citing works jumped 36-fold, from 13 to 476.

Juvenile Hormone Research

Figure 3 is a series of research specialties that emphasize the synthesis and the role of hormones on the growth and development of insects, including cockroaches. The data indicate that sustained high levels of research and published work on cockroach juvenile hormones, as well as efforts in creating man-made analogs of these, took place from 1985 through 1987. According to the historiograph, more recent specialties concentrate on this trend, especially on the artificial hormonal analog precocene. Precocene is an anti-juvenile hormone found in plants that induces irreversible precocious metamorphosis and sterilization in insects (such as grasshoppers and locusts) by suppressing the function of the corpora allata gland, which plays a major role in vitellogenin synthesis.[33] However, precocene has very limited effects on cockroaches—in the nymphal stage, the insects are not sensitive to precocene when exposed to practical doses of the chemical.[3]

Conclusion: Will Cockroaches Have the Last Laugh?

While scientists are endeavoring to control cockroach populations with an arsenal of nerve toxins, hormone and biochemical regulators, and pheromonal lures, in the end the roaches may yet become inheritors of the planet. A glimpse of this possibility can be found in the field of radiobiology, where scientists are interested in measuring the ability of living organisms to tolerate varying levels of radiation, based on a unit called a roentgen (measure of energy equal to 100 ergs per gram of irradiated material), also known as a "rad" or "rem." A "rem" stands for *r*oentgen *e*quivalent *m*an—the dosage that will cause a specifically measured amount of injury to human tissue.[34] A "rad" is used for equivalent exposures for nonhuman living tissue.

Radiobiologists have found that humans can safely withstand a one-time exposure of 5 rems or less (most people are exposed to only 16 rems in their lifetime), while a lethal dose is 800 rems or more.[34] In experiments conducted during the 1950s on gamma-radiation effects, insect researchers found—in contrast—that the cockroach's lethal dosage was horrifically higher—for the American cockroach, 67,500 rads; for the German cockroach, between 90,000 and 105,000 rads.[35] The amount of radiation roaches can withstand is equivalent to that of a thermonuclear explosion![36] It is humbling to think that such a lowly creature may survive the human race in the event of a nuclear holocaust.

* * * * *

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