PREVALENCE AND MAGNITUDE OF RESISTANCE TO CYCLODIENE AND PHENYLPYRAZOLE INSECTICIDES IN *BLATTELLA GERMANICA* AND *DROSOPHILA MELANOGASTER*

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Abstract - The utility of fipronil and perhaps other phenylpyrazoles for German cockroach, *Blattella germanica*, control may be affected by resistance to cyclodienes in field populations, because of cross resistance between these two classes of insecticides. Field populations of *B. germanica* were sampled for the presence of chlordane resistance, and to determine whether chlordane resistance confers cross-resistance to fipronil in these populations. Additional screening experiments with fipronil and JKU 0422 were also performed on cockroaches, and a strain of *Drosophila melanogaster* (Meigen) that shows high levels of cyclodiene resistance. Six field strains of German cockroach were collected from household populations in Virginia, USA. Physiological resistance was detected in all the strains; resistance ratios ranged from RR = 3 to RR = 33. The data indicate the potential for the presence and variability of chlordane resistance in the field. However, there was no indication of cross-resistance to the phenylpyrazoles fipronil or JKU 0422 in field strains. The strain of *D. melanogaster* showed 35-fold resistance to fipronil. Relatively low resistance to fipronil and high resistance to JKU 0422 was observed in cyclodiene-resistant laboratory strains of *B. germanica* and *D. melanogaster*. The structural dependence of this large difference apparently resides in the chemical substituents at the 3 and 5 position on the pyrazole ring. Cyclodiene resistance is primarily due to a specific mutation of Ala to Ser at position 302 in a GABA receptor subunit gene, and this mutation has been found in a number of cyclodiene-resistant insect species. Additional polymorphisms are found in cyclodiene-resistant strains of *B. germanica*. We hypothesize that two mechanisms of resistance are present, with the mechanism providing the highest level of resistance being an altered GABA receptor, whereas the lesser of the mechanisms may be enhanced oxidative detoxication of chlordane.
Key words - Cockroach, fipronil, cross-resistance, chlordane, GABA receptor.

INTRODUCTION

Chlordane (Figure 1) was one of the first modern insecticides used for control of the German cockroach, *Blattella germanica* (L.). Its effectiveness led to extensive use and within a few years control-failure resistance developed (Bedingfield, 1952). Topical application methods estimated 200-fold chlordane resistance in some field populations (Heal *et al.*, 1953), and resistance extended to other cyclodiene insecticides, including dieldrin, heptachlor, and lindane (Fisk and Isert, 1953; Grayson, 1954; Butts and Davidson, 1955). Moderate to high levels of resistance have remained in some field populations, although there has been little or no use of chlordane for German cockroach control in the last 30 years (Bennett and Spink, 1968; Nelson and Wood, 1982).

The persistence of chlordane resistance in these populations may be important to the efficacy of new insecticides that have a similar mode of action. The insecticide fipronil (Fig. 1) is a phenylpyrazole, and this class of compound blocks chloride permeability of the gamma-aminobutyric acid (GABA) receptor, as do the cyclodienes (Bloomquist, 1996). The utility of fipronil and perhaps other phenylpyrazoles for German cockroach control may be affected by resistance to cyclodienes in field populations, because of the potential of cross resistance between these two classes of insecticides (Bloomquist, 1993). Valles *et al.* (1997) reported that enhanced physiological tolerance to dieldrin and lindane in laboratory strains of *B. germanica* may also extend tolerance to fipronil. To date, there is little information on the activity of fipronil in dieldrin-resistant or tolerant laboratory strains of *B. germanica*. A laboratory strain, which was artificially selected for high-level dieldrin resistance, showed only limited resistance (7.7-fold) to fipronil (Scott and Wen, 1998), but high level resistance (553-fold) to the structurally related phenylpyrazole JKU 0422 (Figure 1) was observed (Bloomquist, 1994).

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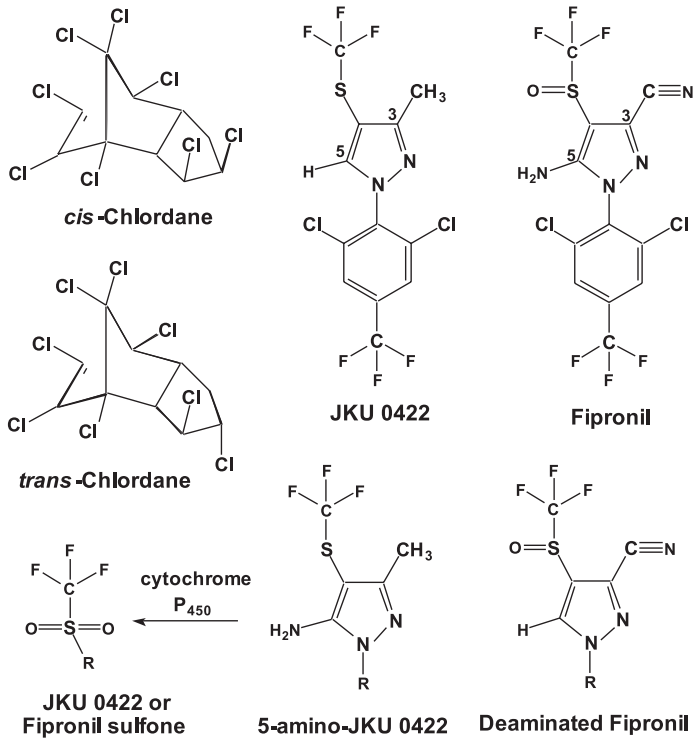

Figure 1. Chemical structures of compounds referred to in the text. Parent compounds are shown in the top row. The sulfone metabolites of JKU 0422 or fipronil that arise from oxidation by cytochrome P_{450} monooxygenases.

Because there is little current data on the extent and distribution of chlordane resistance in field populations, or the potential for these strains to develop cross-resistance toward fipronil, investigation of these phenomena would provide practical information on the frequency and stability of cyclodiene resistance in the field, and the potential for long-term utility of fipronil for German cockroach control. The specific objectives of the research presented here were to sample several field populations of *B. germanica* for the presence of chlordane resistance, and to determine whether chlordane resistance confers cross-resistance to fipronil in these populations. Additional screening experiments with fipronil and JKU 0422 were also performed on cockroaches, as well as a laboratory strain of *Drosophila melanogaster* (Meigen) that shows high levels of cyclodiene resistance (Bloomquist, 1993). These studies were aimed at elucidating the magnitude and mechanisms of cross resistance and its chemical structural dependence among related phenylpyrazoles.

MATERIALS AND METHODS

Chemicals

Fipronil (97% purity) was supplied by Rhone Poulenc Ag Co., Research Triangle Park, North Carolina. Technical chlordane, (70% purity) was from Velsicol, Chicago, Illinois. Historically, the purity of chlordane samples is expressed as the percentage of *cis*- and *trans*-chlordane (Figure 1), with the remainder composed of related chlorinated bicyclics (Bloomquist, 1998). The JKU 0422 used in this study had a purity of 98% and was supplied by Bayer AG, Monheim, Germany.

Insects

A susceptible strain (VPI or CSMA) of German cockroaches was used as a comparative standard to determine resistance ratios (RR). Field strains (Landsdown, Lincoln Terrace, Manor, Peters, Port, and Willow) of cockroaches were collected in 1997 from household populations at several locations in Vir-

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ginia. The Landsdown and Lincoln Terrace strains were collected in apartment buildings built in 1952 and since then treated for cockroaches by the Roanoke Redevelopment and Housing Authority. The Peters strain was collected from a household in which the resident previously lived in the Lincoln Terrace apartments. The Portsmouth strain was from apartments built in the 1960s and managed by the Portsmouth Redevelopment and Housing Authority; the Manor strain was from apartments in Richmond; and the Willow strain was from apartments in Virginia Beach. The susceptible CSMA strain was provided by Jeff Scott, Cornell University. All cockroaches collected from the field were reared at 27 $\pm$ 2 ºC, 60 $\pm$ 10% RH, and a photoperiod of 12:12 (L:D). Each strain was maintained in glass containers with harborage, rat chow, and water, *ad libitum*. Susceptible (Oregon-R) and cyclodiene-resistant (RDL) strains of *D. melanogaster*, reared in plastic vials on artificial media (Bloomquist, 1994), were kindly donated by Doug Knipple, Cornell University, Ithaca, New York.

Bioassays

Insecticide dilutions were prepared from technical grade materials dissolved in acetone. The LD_{50} (micrograms or nanograms per cockroach) was estimated by applying 1 microliter aliquots of 5-8 concentrations of insecticide, producing from 1-99% mortality, to the ventral mesothorax of anesthetized male cockroaches. Each concentration was typically replicated three times with 10 cockroaches in each replicate. Treated cockroaches were moved to a clean surface and provided water. Mortality was recorded in 24 h for phenylpyrazoles and 72 h for chlordane due to its slow action. Toxicity data were subjected to probit analysis (SAS Institute, 1982). Resistance ratios (RR) were calculated by the formula: LD_{50} field strain/LD_{50} VPI or CSMA.

Toxicity bioassays on *D. melanogaster* used a surface-contact method. Test compounds were dissolved in acetone and a 150 ml aliquot of this solution was applied to glass vials that were evenly coated by rotating the vial while the solvent evaporated. Adult female flies were then added to the vials, which were stoppered with dental wicks containing a 10% sucrose solution. Mortality was scored 24 h later and analyzed by computerized probit analysis, with RR calculated as described above.

RESULTS

Physiological resistance to chlordane was detected in virtually all of the field strains of *B. germanica* collected for this evaluation. Regression of the available data in a linear model gave resistance ratios that ranged from RR = 3 in the Landsdown strain to RR = 33 in the Willow strain (Table 1). The overlap in the confidence intervals with the susceptible (VPI) strain indicates a low level of resistance in the Landsdown strain that may not be statistically significant. Although the Landsdown and Lincoln Terrace apartments were constructed at the same time, and presumably received nearly similar cockroach-control treatments, the level of chlordane resistance in these two populations was significantly different. Based on the observed overlap in confidence limits across all the strains, the rank order of resistance across was Willow = Lincoln = Peters = Port > Manor > Landsdown. Although the sample number of pest populations was small, these data indicate the potential for the presence and variability of chlordane resistance in the field.

The field strains showed heterogeneous responses (low slope value) in some cases, and this phenomenon is epitomized by the response of the Lincoln strain (Figure 2). In this case, the dose was varied over a 30-fold range, but the toxicity never exceeded 79%. The toxicity was essentially flat between a dose of 2 and 15 mg/insect (40-60% lethality) and then increased again at higher doses (Figure 2). Assuming the responses for resistant individuals had two components, represented by the lines A and B in Figure 2, the LD_{50}s for these 2 types of responses in the Lincoln strain would be about 3 mg/insect (line A) and 17 mg/insect (line B), and the RRs would be 10 and 57, respectively.

Fipronil proved to be about 50-fold more toxic to the VPI strain than chlordane, and in contrast to the significant levels of resistance to chlordane observed in field strains of *B. germanica*, there was little cross resistance observed to fipronil (Table 2). The resistance ratios ranged from a low of 1.7 to a high

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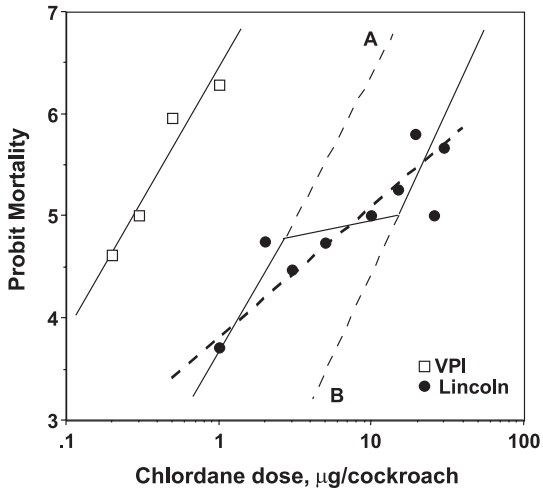

Figure 2. Toxicity of chlordane to susceptible (VPI) and chlordane-resistant (Lincoln) strains of *B. germanica*. Mortality is expressed as probit values (ordinate). Thin solid lines are drawn through the data points of CSMA (open squares) and Lincoln (filled circles). The heavy dashed line indicates the calculated response relationship for Lincoln. The light dashed lines A and B are the hypothetical parallel responses of resistant populations in the Lincoln strain.

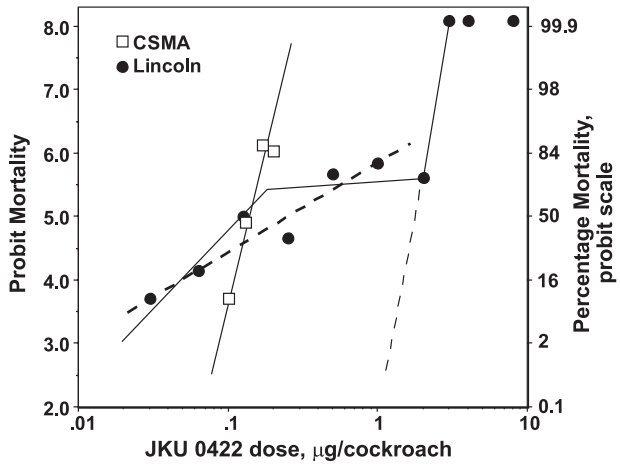

Figure 3. Toxicity of JKU 0422 to susceptible (CSMA) and chlordane-resistant (Lincoln) strains of *B. germanica*. Mortality is expressed equivalently as probit values (left ordinate) and as percentage mortality on a probit scale (right ordinate). Thin solid lines are drawn through the data points of CSMA (open squares) and Lincoln (filled circles). The heavy dashed line indicates calculated response relationship of the lowest 6 doses for Lincoln. The light dashed line is the hypothetical parallel response of resistant individuals in the Lincoln strain.

of 2.4 in the Lincoln and Manor strains, respectively. Based on the lack of overlap in the confidence limits, the resistance appears to be statistically significant, but of low magnitude. Responses to fipronil in the field strains was also more homogenous, based on the greater slope values for the response lines, and displayed little evidence of being a mixed population.

Surface-contact bioassays with a dieldrin-resistant strain of *D. melanogaster* observed higher levels of fipronil resistance than that observed in the German cockroach (Table 3). In this case, the RR was 35. This level of resistance is 15- to 20-fold greater than that measured in the cockroach field strains, and is probably related to the fact that this strain was selected for dieldrin resistance. Additional studies with the structurally-related phenylpyrazole JKU 0422 in *D. melanogaster* found much higher levels of resistance (RR = 1253). In terms of its comparative toxicity, JKU 0422 was 5 times as toxic to the susceptible Oregon-R strain compared to fipronil and the slopes of the response lines were generally greater as well (Table 3).

The differential sensitivity of fipronil and JKU 0422 in laboratory strains *B. germanica* and *D. melanogaster* led us to study responses to JKU 0422 in one of our field strains (Lincoln). Bioassay of JKU 0422 in the susceptible CSMA strain and Lincoln strain is shown in Figure 3. Response in the susceptible strain to topical application to JKU 0422 had a steep slope (8.6 ± 1.7), with an LD_{50} of 0.14 mg and 95% confidence interval of 0.11 - 0.17. Thus, the topical insecticidal activity of JKU 0422 was about twice that of chlordane, but 24-fold less than that of fipronil (Table 1). The dose-response relationship of the Lincoln strain was more complicated, and again showed significant heterogeneity, with doses spanning nearly 2 orders of magnitude required to cover the response spectrum (Figure 2). At low doses of JKU 0422 (0.03 and 0.06 mg/insect), mortality in the Lincoln strain was actually greater than that of the CSMA strain. Toxicity increased linearly at higher doses, but showed a plateau of 80% mortality at doses from 0.5 - 2 mg/insect. This type of response is indicative of a mixed population containing resistant individuals. Modeling the data as a single response line based on the 6 lowest doses gave a slope of 1.3 ± 0.3, an LD_{50} of 0.24 mg (0.15 - 0.0.38), and a RR = 1.7. JKU 0422-induced mortal-

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Table 1. Toxicity parameters of susceptible (VPI) and field strains of German cockroaches treated with chlordane.

Strain	Slope ± SE	LD_{50}, mg/insect (95% CI)	RR
Willow	2.0 ± 1.0	9.9 (5.0 - 19.8)	33
Lincoln	1.0 ± 0.3	8.5 (4.4 - 16.3)	28
Peters	2.6 ± 1.1	7.0 (4.4 - 11.0)	23
Portsmouth	2.7 ± 0.9	6.8 (4.8 - 9.7)	23
Manor	1.4 ± 0.3	2.4 (1.0 - 5.5)	8
Landsdown	1.9 ± 0.5	0.9 (0.3 - 2.5)	3
VPI	2.9 ± 0.8	0.3 (0.2 - 0.5)	—-

Table 2. Toxicity parameters of susceptible (VPI) and field strains of German cockroaches treated with fipronil.

Strain	Slope ± SE	LD_{50}, ng/insect (95% CI)	RR
Lincoln	5.3 ± 1.1	10.2 (9.0 - 11.5)	1.7
Manor	5.2 ± 1.5	14.4 (12.0 - 17.4)	2.4
Landsdown	3.1 ± 1.1	10.5 (8.2 - 13.6)	1.8
VPI	4.0 ± 1.1	5.9 (4.4 - 7.8)	—-

Table 3. Toxicity parameters of a susceptible (Oregon-R) and a highly selected, dieldrin-resistant (RDL) strain of *D. melanogaster* to JKU 0422 and fipronil.

Strain	Compound	Slope ± SE	LC_{50}, ng/cm^2 (95% CI)	RR
RDL	JKU 0422	5.1 ± 0.91	1629 (1234 - 2150)	1253
Oregon-R	JKU 0422	10.3 ± 1.9	1.27 (1.17 - 1.35)	—-
RDL	fipronil	3.8 ± 1.1	224 (115 - 435)	35
Oregon-R	fipronil	2.3 ± 0.4	6.4 (4.27 - 9.87)	—-

ity reached 100% at doses of 3, 4, and 8 mg/insect, with 20 insects total treated at these doses (Fig. 3). Assuming a response line for resistant individuals that is parallel to that of CSMA and reflected in the toxicity at 2 and 3 mg/insect, would yield an LD_{50} of about 1.9 mg and give a RR = 14.

DISCUSSION

Chlordane resistance was common in field strains of German cockroach collected in Virginia. Five out of the six strains evaluated had statistically significant levels of resistance to this compound, that would probably increase in magnitude rapidly under selection pressure. The presence of chlordane resistance in *B. germanica* field populations has been documented several times during the last 40 years (Bennett and Spink, 1968; Brown, 1958; Keller *et al.*, 1956; Nelson and Wood, 1982). In addition, Keller *et al.* (1956) reported that chlordane resistance in a laboratory colony gradually diminished in the absence of exposure, and within 5 years the strain reverted to normal susceptibility. However, Grayson (in Brown, 1958) reported persistence of chlordane resistance after 14 generations without exposure.

The rate of regression of resistance in a field population is variable and may depend on features such as the degree of fitness of resistant individuals, the exposure history, and the size and degree of isolation of the population. The fitness of chlordane-resistant individuals may provide some basis for the persistence of this trait in populations, but Grayson (1954) reported no biological advantages, such as increased nymphs per egg case or body weight, for chlordane-resistant strains of *B. germanica*. There is no information on the use of chlordane for cockroach control in the Lincoln Terrace and Landsdown apartments, but this insecticide may have been used in these apartments after resistance was reported in other parts of the country. Alternatively, these insects may have come into contact with persistent cyclodiene residues used for termite control. The history of the Lincoln Terrace and Landsdown apartment complexes are similar, and although they are only about 8 km apart, the level of chlordane resistance differed greatly. Apparently, their exposure to chlordane or features that isolated the two populations of *B. germanica*, such as movement of residents between Lincoln Terrace and Landsdown apartments, were different and resulted in the levels of chlordane resistance we observed.

The potential for household infestations and accompanying insecticide resistance in *B. germanica* to spread in urban environments is demonstrated in the Lincoln Terrace and Peters strains. The Peters strain originated from individual cockroaches collected in an independent dwelling, and the homemaker had moved from Lincoln Terrace apartments several months previously. Thus, if these strains are related, they should have a similar sensitivity to chlordane. This result was observed, and the confidence intervals around the LD_{50}s in the Lincoln and Peters strain also overlapped. These results suggest that the Peters strain apparently originated from individuals in the Lincoln Terrace apartments. Molecular genetic analysis of individuals of each population would provide important confirmatory evidence for this conclusion.

The chlordane resistance in the strains evaluated here may be representative of the range and variability expected in the field; however, in the absence of selection, there was no indication of strong cross resistance to fipronil or JKU 0422 in field strains. Valles *et al.* (1997) suggested that cross resistance to fipronil may occur in *B. germanica* strains showing tolerance to cyclodienes. They reported that a lindane- and dieldrin-tolerant strain was significantly more tolerant (1.6 times at the LD_{50} level) to fipronil compared with a susceptible strain. Scott and Wen (1998) found that a dieldrin-resistant (LD_{50} RR >17,000) strain was 7.7 fold resistant to fipronil, but concluded that this level of resistance would not influence the efficacy of this material under field conditions. This report stands in contrast to that of Bloomquist (1994), where over 553-fold resistance to topically applied JKU 0422 was observed in the same strain. On this basis, it was concluded that cyclodiene-resistance in the field might provide a high level of cross resistance to phenylpyrazoles. The resistance to JKU 0422 in the Lincoln strain appears to be about 40-fold less than that observed in the LPP strain by Bloomquist (1994), but may increase in the presence of selection pressure. In general, it appears that flies show greater cross resistance to fipronil than cockroaches. In the present study, the RDL strain of *D. melanogaster* showed 35-fold resistance to fipronil, compared to $\leq$ 3-fold in our field strains of *B. germanica* or the 7.7-fold resistance to fipronil observed by Scott and Wen (1998). Similarly, Colliot *et al.* (1992) observed 90-fold resistance to fipronil in a strain of housefly that displayed 2900-fold resistance to dieldrin.

Relatively low resistance to fipronil and high resistance to JKU 0422 was observed in cyclodiene-resistant laboratory strains of *B. germanica* and *D. melanogaster*. The structural dependence of this large difference apparently resides in the chemical substituents at the 3 and 5 positions of the pyrazole ring (Figure 1). The structure-activity relationship of the resistance could be addressed by measuring the toxicity of 5-amino-JKU 0422 and deaminated fipronil (Figure 1). The methyl group in the 3 position of JKU 0422 is a tetrahedral moiety, unlike the narrow and electron-rich cyano group present in fipronil (Figure 1). In addition, the presence of the 5-amino group in fipronil provides the possibility of hydrogen bonding at this position, which could account for the greater toxicity of fipronil in cockroaches through a more avid interaction with the GABA receptor, especially the cyclodiene-resistant Ser isoform (see below). Although JKU 0422 was more toxic than fipronil in a surface-contact bioassay with *D. mela-*

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nogaster (Table 3), this effect may have been due to fipronil's tendency to stick to glass, since solutions of this material held in glass vials tended to lose activity over several days (unpublished observation). The large difference in resistance between JKU 0422 and fipronil in light of their structural similarity is reminiscent of target site resistance to pyrethroids, where super-*kdr* resistance provides several hundred fold resistance to a-cyano containing pyrethroids, but only about 30- to 50-fold resistance to structurally similar pyrethroids lacking an a-cyano group (Sawicki *et al.*, 1986).

Cyclodiene resistance is primarily due to a specific mutation of Ala to Ser at position 302 in a GABA receptor subunit gene (ffrench-Constant *et al.*, 1993), and this mutation has been found in a number of cyclodiene-resistant insect species (ffrench-Constant *et al.*, 1995). Additional polymorphisms are found in cyclodiene-resistant strains of *B. germanica* (Kaku and Matsumura, 1994), and it is interesting that there appeared to be two mechanisms of chlordane resistance operating in the Lincoln strain, since the resistant toxicity responses seemed to fall on two different lines (Figure 2). We hypothesize that two mechanisms of resistance are present, with the mechanism providing the highest level of resistance being an altered GABA receptor (line B, Figure 3), whereas the lesser of the mechanisms may be enhanced oxidative detoxication of chlordane (line A, Figure 3). Oxidative degradation of chlordane, especially the *trans* isomer (Fig. 1), is known to occur in mammals (Aizawa, 1982), and the mixed function oxidase inhibitor, piperonyl butoxide, was able to partially reduce resistance to chlordane in the Muncie 86 strain of *B. germanica* (Scharf *et al.*, 1996). An elevated oxidative capacity of the Lincoln strain would explain the higher than anticipated toxicity of low doses of JKU 0422 (Fig. 3), because sulfoxidation to the sulfone (Fig. 1) is known to occur with fipronil (Hainzl *et al.*, 1998) and is a bioactivation reaction that increases toxicity. Similarly, Valles *et al.* (1997) reported that fipronil toxicity is antagonized by co-application of piperonyl butoxide. Thus, oxidative metabolism to the sulfone is also likely to occur with JKU 0422 and to have the same enhancing effect on its toxicity. Future studies should address in more detail the issue of metabolic vs. target site resistance mechanisms to chlordane and phenylpyrazoles in the Lincoln strain.

ACKNOWLEDGEMENTS

The authors would like to thank Bob Barlow, Becky Barlow, and Greg Polsinelli for technical assistance with the bioassays. Financial support was provided by Rhone-Poulenc Ag Co., FMC Corp., and the Biological Sciences Initiative of Virginia Tech.

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