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Jan Święch

APPLICATION OF MULTIDIMENTIONAL ANALYTIC GEOMETRY TO THE ESTIMATION OF THE EFFECT OF JOINT ACTION OF INSECTICIDES IN MIXTURES

I. INTRODUCTION

The effect of the action of insecticide on the organism of an insect (R = reaction) is a function of the applied dose of insecticide (D = dose). R = f(D). We expect that after mixing insecticides the effect of the action of the mixture (Rm) will be a function of the sum of doses of insecticides (Dm): R_m = f(Dm) (= addition).

However, the effect of the action of mixtures — as the result of joint action of insecticides in the process of intoxication of the organism of an insect — can be higher then the expected effect: Rm > f (Dm) (= synergism) or lower: Rm < f (Dm) (= antagonism).
In view of the practical aspect of synergism there are used various methods in studies on mixtures of insecticides, tending towards quantitative assesment of the effect of joint action of the components of these mixtures in the shape of so-called coefficient of synergism (Bakuniak, 1973; Cole and Clark, 1962; Gowing, 1960; Sun and Johnson, 1960; Tammes, 1964).

These methods are generally limited to studies on two-component mixtures. The autor proposes the application of multimentional analytic geometry to calculate the effect of joint action of any number of insecticides in mixture.

II. METHOD

To evalutate the interaction of insecticides in n-component mixtures we can apply the method of multidimentional analytic geometry. We consider the n-component mixture of insecticides as a set of systems (LD_1, LD_2, LD_3, ... , LD_n) in n-dimentional Cartesian space C_n, where: LD_i — 'dosis letalis' of this i-of insecticide stated for instance by Finney (1952) or Litchfield and Wilcoxon (1949; see: Bojanowska, 1961).

And thus, the individual toxicity of the particular insecticides create in space C_n following sets:

$$
\begin{array}{llllll}
I_1 & (LD_1, & 0, & 0, & \ldots, & 0) \\
I_2 & (0, & LD_2, & 0, & \ldots, & 0) \\
I_3 & (0, & 0, & LD_3, & \ldots, & 0) \\
\cdot & \cdot & \cdot & \cdot & \ldots, & \cdot \\
\cdot & \cdot & \cdot & \cdot & \ldots, & \cdot \\
\cdot & \cdot & \cdot & \cdot & \ldots, & \cdot \\
I_n & (0, & 0, & 0, & \ldots, & (LD_n),
\end{array}
$$

and the toxicity of these insecticides in the mixture create in C_n the set:

$$M\,(LDm_1, LDm_2, LDm_3, \ldots, LDm_n).$$

The sets I_1, I_2, I_3, ... , I_n delimit in the space C_n the (n-1)-dimentional hyperspace wchich designates the expected effect of the joint action of n insecticides in mixture (= addition). This hyperspace is describerd by the equation (1):

$$
(1) \qquad 0 = \begin{vmatrix}
LDm_1 - LD_1 & LDm_2 & LDm_3 & \ldots & LDm_n \\
-LD_1 & LD_2 & 0 & \ldots & 0 \\
-LD_1 & 0 & LD_3 & \ldots & 0 \\
\cdot & \cdot & \ddots & \ldots & \cdot \\
\cdot & \cdot & \cdot & \ldots & \cdot \\
\cdot & \cdot & \cdot & \ldots & \cdot \\
-LD_1 & 0 & 0 & \ldots & LD_n
\end{vmatrix} \leftrightarrow
$$

$$\leftrightarrow LDM_1LD_2LD_3 \cdot \ldots \cdot LD_n + LDm_2LD_1LD_3 \cdot \ldots \cdot LD_n + LDm_3LD_1LD_2 \cdot \ldots \cdot LD_n + LDm_nLD_1LD_2 \cdot \ldots \cdot LD_{n-1} - LD_1LD_2LD_3 \cdot \ldots \cdot LD_n = 0.$$

Denoting LDm_i by x_i and the succeding products LD_i with LDm_i by A_1, A_2, A_3, ... , A_n and the product $LD_1LD_2LD_3 \cdot \ldots \cdot LD_n$ by A_0 we optain the equation of hyperspace H_{n-1} in the general form (2) (Borsuk, 1976):

$$(2) \qquad A_1 x_1 + A_2 x_2 + A_3 x_3 + \ldots + A_n x_n - A_0 = 0.$$

In the instance of addition, after substition for the equation of the hyperspace H_{n-1} of the adequate values LD_i and LDm_i, it satisfies the equation (2). Taking the value of addition as the unity (= 1) the coeficient of the joint action of insecticides in the mixture equals (3):

$$(3) \qquad WW = \frac{A_0}{A_1 x_1 + A_2 x_2 + A_3 x_3 + \ldots + A_n x_n},$$

when: WW = 1 -addition,
WW > 1 -synergism,
WW < 1 -antagonism.

For instance, the formula for calculation of the index WW in the mixture of three insecticides has the form (4):

$$WW = \frac{LD_1 LD_2 LD_3}{LDm_1 LD_2 LD_3 + LDm_2 LD_1 LD_3 + LDm_3 LD_1 LD_2} \tag{4}$$

and in the instance of the mixture of two insecticides (5):

$$WW = \frac{LD_1 LD_2}{LDm_1 LD_2 + LDm_2 LD_1} \tag{5}$$

or in the instance of the mixture of one insecticide with a synergist which itself does not show any insecticidal activity (6):

$$WW = \frac{LD_1}{LDm_1}. \tag{6}$$

The significance of appearance of synergism in the mixture of insecticides we can test at the accepted level of probability the significance of the average result | WW-1 |, for instance out of five repetitions. The Dunnet's two-sided test (Dunnet, 1955) is the most applicable. The autor proposes the program 'MIX' (to the microcomputer ZX Spectrum Sinclair) to calculate the effect of joint action of insecticides in mixtures.

III. EXAMPLE

The three component mixture containing 10% of Insecticide No. 1+ +50% of Insecticide No. 2+40% of Insecticide No. 3. The calculation of results of the investigation on synergism of the mixture are presented in Table 1.

Program ,MIX' to calculate the effect of joint action of insecticides in mixture to the microcomputer ZX SPECTRUM:

```
1Ø  REM ,MIX': Joint action of insecticides
2Ø  REM ZX SPECTRUM 48 K
3Ø  CLS: INPUT "Number of insecticides" ' "in mixtures?";
    n' "Number of repetitions?"; r: DIM a(r): DIM b(r, n): DIM c(r, n):
    DIM d(n) : DIM m(r) : DIM p(n) : DIM x(r) : DIM z(r)
4Ø  LET s1 = Ø: FOR j = 1 TO n: INPUT ("Percentage ";j; "-insecticide") ; "in mixture?" ; p(j) : LET s1 = s1+p (j) : IF s1 = 1ØØ
    THEN GO TO 6Ø
5Ø  BEEP .2,17.6: BEEP .3,13.4: PRINT FLASH 1; AT 12,12; "Sum<>
    1ØØ!": GO TO 4Ø
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Table 1

The results of the investigation on synergism of the mixture of insecticides: Ins. No. 1 — 10%, Ins. No. 2 — 50% and Ins. No. 3 — 40%.
LD_{50} microgram per insect

Insecticide	LD_i	Repetitions				
		1	2	3	4	5
Ins. No. 1:	LD_1	0,21	0,19	0,24	0,19	0,22
Ins. No. 2:	LD_2	0,67	0,54	0,60	0,72	0,66
Ins. No. 3:	LD_3	1,60	1,58	1,46	1,60	1,63
Mixture 1:5:4	LDm	0,27	0,25	0,30	0,22	0,24
LDm. 0,1	LDm_1	0,027	0,025	0,030	0,022	0,024
LDm. 0,5	LDm_2	0,135	0,125	0,150	0,110	0,120
LDm. 0,4	LDm_3	0,108	0,100	0,120	0,088	0,096
Index	WW	2,52	2,35	2,19	3,03	2,86

WW = 2.59; s = 0.351; S_{ww} = 0.157;
Confidence interval — p = 0.95 : 0.157 · 3,88 = 0.610;
— p = 0.99 : 0.157 · 5.73 = 0.900;
WW—1 = 2.59—1 = 1.59 > 0.900.
Result: Significance of synergism at p = 0.99.

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6Ø CLS: FOR i = 1 TO r: PRINT AT 21, Ø; i; "-repetition:": INPUT "LD50 of mixture?"; m(i) : FOR j = 1 TO n: INPUT ("LD50 o f"; j; "-insecticide?"); b(i, j): NEXT j: NEXT i: CLS: FOR i = 1 TO r: LET a(i) = 1: FOR j = 1 TO n: LET a(i) = a(i) * b(i, j): LET c(i, j) = m(i) * p(j)/1ØØ : NEXT j: NEXT i: FOR i = 1 TO r: LET z(i) = Ø:FOR j = 1 TO n: LET d(j) = 1: LET e = b (i, j): LET b(i, j) = c(i, j): FOR k = 1 TO n: LET d(j) = d(j) * b(i, k): NEXT k: LET b i, j = e: LET z(i) = z(i)+d(j): NEXT j: NEXT i: LET s1 = Ø: LET s2 = Ø: FOR i = 1 TO r: LET x(i) = a(i)/z(i): LET s1 = s1+x(i): LET s2 = s2+x(i) * x(i): NEXT i: IF r = 1 THEN GO TO 8Ø
7Ø LET s = SQR ((s2−s1 * sl/r)/(r−1)): GO TO 9Ø
8Ø LET s = Ø
9Ø LET SWW = s/SQR r: LET WW = s1/r: CLS : PRINT TAB 5; "INDEX OF JOINT ACTION:" : FOR i = 1 TO r: PRINT AT i+1, 8; "WW("; i;") = "; x(i) : NEXT i: PRINT 'TAB 8; "MEAN: ";WW: INPUT#Ø; "Dunnet's two-sides test?" ' "to.o5 = "; d1, "to.o1 = "; d2: LET C1 = SWW * d1: LET C2 = SWW * d2: PRINT' 'TAB 7; "CONFIDENCE INTERVAL": 'TAB 6; "at p = 0.95: "; C1'TAB 6; "at p = 0.99: "; C2: LET a$ =" ANTAGONISM": LET s$ =" SYNERGISM": LET c$ =" Significance of": LET p$ =" at p = 0.95": LET q$ = "at p = 0.99": IF C1 ⟩ = ABS (WW-1) THEN PRINT FLASH 1;'"ADDITION": GO TO 15Ø
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100 IF C2 ( ABS (WW-1) THEN GO TO 130
110 IF WW ( 1 THEN PRINT FLASH 1'c$ + a$'p$: GO TO 150
120 PRINT FLASH 1'c$ + s$'p$: GO TO 150
130 IF WW ( 1 THEN PRINT FLASH 1'c$ + a$'q$: GO TO 150
140 PRINT FLASH 1'c$ + s$'q$: GO TO 150
150 PRINT # 0; "START-press 's'", "END-press 'e'": PAUSE 0: IF
    INKEY$ = "s" OR INKEY$ = "S" THEN RUN
160 IF INKEY$ = "e" OR INKEY$ = "E" THEN NEW
170 GO TO 150
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Jan Święch

ZASTOSOWANIE GEOMETRII ANALITYCZNEJ WIELOWYMIAROWEJ DO OCENY EFEKTU WSPÓŁDZIAŁANIA INSEKTYCYDÓW W MIESZANINACH

STRESZCZENIE

Do obliczeń efektu interakcji insektycydów w mieszaninach (addycja, synergizm, antagonizm) zaproponowano metodę geometrii analitycznej wielowymiarowej. Mieszanina n-składnikowa traktowana jest jako zbiór

układów (LD_1, LD_2, LD_3, ..., LD_n) w n-wymiarowej przestrzeni kartezjańskiej C_n. Toksyczności indywidualne poszczególnych insektycydów tworzą w C_n układy I_1 (LD_1, O, ..., O), I_2 (O, LD_2, O, ..., O), I_3 (O, O, LD_3, ..., O), ..., I_n (O, O, O, ..., LD_n), zaś toksyczności ich w mieszaninie tworzą w C_n układ M (LDm_1, LDm_2, LDm_3, ..., LDm_n).

Układy I_i wyznaczają w C_n hiperpłaszczyznę (n-1)-wymiarową określającą oczekiwany efekt współdziałania n insektycydów w mieszaninie (addycja). Hiperpłaszczyzna H_{n-1} opisana jest równaniem ogólnym: $A_1x_1 + A_2x_2 + A_3x_3 + ... + A_nx_n = 0$. Przyjmując indeks addycji WW = 1 otrzymamy: $WW = A_0/A_1x_1 + A_2x_2 + A_3x_3 + ... + A_nx_m$. Gdy WW ⟩ 1 — synergizm, gdy WW ⟨ 1 — antagonizm.

Istotność synergizmu bada się testując istotność różnicy $|WW-1|$ według Dunneta (1955).

Podano wzory na obliczanie wskaźników WW mieszaniny dwu- i trójskładnikowej oraz dla przypadku mieszaniny insektycydu z synergetykiem. Załączono listing programu dla mikrokomputera ZX Spectrum Sinclair obliczającego wartość wskaźnika WW i testującego istotność synergizmu n-składnikowej mieszaniny insektycydów.

Ян Сьвенх

ПРИМЕНЕНИЕ МНОГОРАЗМЕРНОЙ АНАЛИТИЧЕСКОЙ ГЕОМЕТРИИ ДЛЯ ОЦЕНКИ ЭФФЕКТА ВЗАИМОДЕЙСТВИЯ ИНСЕКТИЦИДОВ В СМЕСЯХ

РЕЗЮМЕ

Для вычисления эффекта интеракции инсектицидов в смесях (аддиция, синергизм, антагонизм) предложено метод многоразмерной аналитической геометрии. Смесь н-элементов относится к множеству систем ($ЛД_1$, $ЛД_2$, $ЛД_3$, ..., $ЛД_н$) в н-размерном картеизианском пространстве $С_н$. Личные токсичности отдельных инсектицидов образуют в $С_н$ системы I_1 ($ЛД_1$, 0, ..., 0), I_2 (0, $ЛД_2$, 0, ..., 0), I_3 (0, 0, $ЛД_3$, ..., 0), ..., $I_н$ (0, 0, 0, ..., $ЛД_н$), зато их токсичности в смеси образуют в $С_н$ систему М ($ЛДм_1$, $ЛДм_2$, $ЛДм_3$, ..., $ЛДм_н$).

Системы $I_н$ определяют в $С_н$ гиперплоскость (н-1) — размерную определяющую ожидаемый эффект взаимодействия н инсектицидов в смеси аддиция. Гиперплоскость $Х_{н-1}$ описана общим уравнением:

$A_1x_1+A_2x_2+A_3x_3+ \dots +A_нx_н = 0$. Принимая индекс аддиции WW = 1 получим: $WW = A_0/A_1x_1+A_2x_2+A_3x_3+ \dots A_нx_н$. Когда $WW > 1$ — синергизм, когда $WW < 1$ — антагонизм.

Существенность синергизма исследуется тестируя существенность разницы $(WW-1)$ по Дуннету (1955).

Дано формулы на вычисление показателей WW смеси дву- и триэлементной а также в случае смеси инсектицида с синергетиком. Приложено листинг программы для микрокомпьютера ZX Spectrum Sinclair вычисляющего величину показателя WW и тестирующего существенность синергизма н-элементной смеси инсектицидов.