1 **Agrochemicals, but not other stressors, interact synergistically to increase bee**

2 **mortality**

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17   *Calculation of interaction effect size*

18   Following Jackson *et al*, 2016[1,] the interaction effect size for each observation was calculated as the

19   standardized mean difference (Hedges' d) between the observed value when both stressors were

20   applied in combination and the predicted value should stressors act additively. The latter, *Xp,* was

21   calculated as:

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$$X_p = (X_a - X_u) + (X_b - X_u) + X_u$$

23   where X_a and X_b are the means of treatments a & b and X_u is the mean of the control group (where

24   neither stressor was applied). Hedges' d (d) was calculated as:

25
$$d = \frac{X_o - X_p}{S}j$$

26   where X_o is the observed mean when both stressors were applied in combination, X_p is the predicted

27   mean if stressors act additively, and *j* is a weighting factor based on the number of replicates (n),

28   calculated as:

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$$j = 1 - \frac{3}{4(n_o + n_p - 2) - 1}$$

30   and *S* is the pooled standard deviation calculated as:

$$S = \sqrt{\frac{(n_o - 1)\sigma_o^2 + (n_p - 1)\sigma_p^2}{n_o + n_p - 2}}$$

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32   Where σ_p is the pooled standard deviation for σ_a and σ_b, and n_p is the sum of n_a and n_b. The variance
33   (V_d) of each interaction was calculated as;

$$V_d = \frac{(n_o + n_p)}{n_o n_p} + \frac{d^2}{2(n_o + n_p)}$$

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37   *Example of reversal interaction*

38   Reversal interactions occurred when the effects of the two stressors had contrasting directionality (one

39   positive and one negative effect). For example, exposure to an agrochemical (alone) might decrease

40   worker production, while exposure to a parasite (alone) might increase it. Both of these are plausible

41   effects of biological stressors on bee colonies, reflecting either reduced worker emergence or a switch

42   to investment in rapid but short-lived growth, respectively. Recall that where both main effects are

43   positive, a positive interaction effect indicates synergy, but where both main effects are negative, a

44   negative interaction effect indicates synergy. For reversals such as the example given above, however,

45   the expected sign of a synergistic interaction would be unclear. To resolve this issue, where reversals

46   occurred, we assumed that the largest individual effect observed was the most biologically relevant

47   (following Jackson *et al* [1]). See below for a hypothetical workflow

48   Control colony (X_u): 55

49   Stressor A (agrochemical) (X_a): 30

50   Stressor B (parasite exposure) (X_b): 60

51   We would (based on the above formula) predict an additive interaction (X_p) of 35 workers produced per

52   colony, when bees were exposed to both stressors.

53   If the observed effect of the combined treatment (X_o) was 20 workers produced per colony, then the

54   observed worker output would deviate from the predicted value if effects are additive (X_p) by -15. Given

55   that Stressor A had a larger effect than Stressor B, and that this larger effect was negative, we would

56   invert the final calculated value of *d.*

57   *Analysis of the robustness of results to non-independence within samples*

58   Many of the studies within this analysis included data that were derived from bees kept in groups. For

59   example, Organisation for Economic Co-operation and Development (OECD) recommends that *A.*

60   *mellifera* workers are kept in groups of 10 per cage, with a minimum of 3 cages used per treatment

61   group[2]. This is because *A. mellifera* workers usually die if kept alone. As outlined in the main text, all of

62   the mortality data that originated from caged studies was analysed at the individual level due to a lack

63   of data available at the cage level. The n value for this analysis was calculated using the number of

64   individuals in the treatment group, to match the level that the standard deviation was calculated at.

65   However, as the bees within a cage may experience more similar conditions to those in another cage,

66   this causes potential non-independence of data points. To assess the robustness of our analysis to this

67   issue, we re-ran the analysis of the interactions between stressors on bee mortality using effective

68   sample sizes for data that originated from bees in cages or micro-colonies. Only the analysis of bee

69   mortality was examined for the sensitivity to this assumption because this dataset relied most heavily on

70   data using individual level n values and therefore would be most likely to be affected by non-

71   independence of data points.

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73   We followed the method of Higgins et al.[3], as suggested by Noble et al.[4] to calculate effective sample

74   sizes. For each study that used cages or microcolonies of bees, we extracted information on the number

75   of cages/microcolonies used for each treatment group. This was combined with information on the

76   number of individual bees to calculate the average cluster size (M), where:

77
$$M = \frac{total\ number\ of\ individuals\ across\ all\ treatment\ groups}{total\ number\ of\ cages\ across\ all\ treatment\ groups}$$

78   For example, if a study used cages of 10-12 bees and there were 3 cages of bees in each of the

79   treatment groups (control, stress 1, stress 2, stress 1*stress 2) then:

80
$$M = \frac{30 + 32 + 32 + 34}{3 + 3 + 3 + 3} = \frac{128}{12} = 10.67$$

81   If the number of clusters was unavailable, then these studies were excluded from the re-analysis.

82   The average cluster size was used to calculate the design effect using the formula:

83
$$Design\ effect = 1 + (M - 1) \times ICC$$

84   Where ICC is the intra-cluster correlation coefficient. It was not possible to calculate the ICC for all

85   studies, so we calculated an estimate based on 3 studies for which the appropriate data were available

86   [5–7]. The ICC was calculated in R version 4.0.2, using the iccbin function (using both method A and

87   method B with 1000 Monte-Carlo replicates) from the package aod[8]. This follows the method of

88   Goldstein et al. [9] to partition variance for binary data[9]. The ICC was calculated on individual datasets

89   containing all cages from a single treatment group (n = 35 different treatment groups). From these

90   studies, we found that the ICC ranged from 0 to 0.26 with a median of 0.02 for method A, and from 0 to

91   0.76 with a median of 0.03 for method B. We re-ran our analyses using the maximum ICC values of 0.26

92   and 0.76, as these will have the greatest effect on the sample sizes. An ICC of 0 would be equivalent to

93   our original analysis.

94   Following the example above there would be four ESS calculated for an ICC value of 0.26, each using the

95   same design effect:

96   Design effect = 1 + (10.67 − 1)*0.26 = 3.51

97   Control = 30/3.51 = 8.54

98   Stress 1 = 32/3.51 = 9.11

99   Stress 2 = 32/3.51 = 9.11

100   Stress 1* Stress 2 = 34/3.51 = 9.68

101   The ESS was then used in place of n to calculate Hedges' d. For studies where individuals were kept

102   separately, or only one individual per cage/micro-colony was observed, the n value remained at the

103   individual level. The analysis was then re-run as described above, and the results did not change (Mortality

104   (ICC = 0.26), d = 0.18, CI = 0.08 to 0.28: Mortality (ICC = 0.76), d = 0.16, CI = 0.06 to 0.26 compared with

105   the original estimates of d = 0.19, CI = 0.08 to 0.29), demonstrating the robustness of our original analysis

106   and results to the potential issue of non-independence due to cage effects. For a full breakdown of the

107   sensitivity analysis please see Table S6).

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120 **Table S1. The response variables included in each category and rules for selecting variables when**

121 **multiple measures of a category were available.** Numbers in brackets indicate the number of data points

122 remaining following the removal of 29 effect sizes where it was not possible to determine the interaction

123 type (see methods: statistical analysis).

Category	Dependent variables included	Number of data points	Rules for choosing
Mortality	Proportion of dead colonies/individuals (or 1 - proportion surviving)	192 (172)	Only measures of mortality used. Time point where first treatment group were all dead used, or the final time point if this was not available.
	Total	192 (172)	
Fitness proxies	Sexual production of colony (gynes + males) e.g., number of sexuals, mass of sexuals	2 (1)	Selected if available
	Sexual production of colony (males only) e.g., number of males, mass of males	3 (2)	Selected if gynes+males was not available
	Worker mass (per bee or colony)	12	Selected randomly if sexual production (gynes/males) was not available. Colony size was the maximum size the colony attained across timepoints. Where there were multiple timepoints for ovary length, a timepoint greater than 7 days was selected at random as oocytes can take longer than this to develop.
	Brood production (increase in colony size, area of brood, number of cells, number of eggs, larvae, pupae)	11 (9)	
	Total head protein content[10]	5	
	Ovary development (e.g., ovary length)	3	
	Time until first egg laid	2	
	Lipid:body size ratio[11]	1	
	Sperm viability	1	
	Weight loss over hibernation	1	

Category	Dependent variables included	Number of data points	Rules for choosing
	Emerged queen size (thorax width)	1	
	Sexual maturity rate (%)	1	
	Total	43 (39)	
Behaviour	Sucrose consumption	46 (45)	Random. Where there were multiple timepoints, last timepoint was selected for PER trials but memory tests were selected at random. For sucrose consumption, the timepoint where the control had the greatest consumption was chosen as this is where the greatest difference between treatments was likely to be seen.
	Pollen collection	5	
	Pollen consumption	1	
	Brood removal rate	1	
	Grooming behaviour	3	
	Returning foragers	1	
	Abnormal behaviour	4	
	Flight success/ activity	4	
	Visual learning	1	
	Memory/learning in PER trials	13 (11)	
	Total	79 (76)	
Parasite Load	Parasite load (e.g., viral genome equivalents, number of cells/spores)	38 (37)	Random, where multiple parasites, one was chosen randomly. Where there were multiple timepoints the maximum parasite load was chosen. There is very little information on how parasite dynamics
	Total	38 (37)	

Category	Dependent variables included	Number of data points	Rules for choosing
			affect bee fitness, but we know that for some parasites (*Nosema*, DWV) parasite load is important. This will also be the most comparable metric across different parasite dynamics.
Immune	Phenoloxidase activity	18	Random
	Haemocyte counts	3	
	Lysozyme-like activity in haemolymph	3	
	Immune gene expression (dorsal-1A/toll-like receptor)	2	
	Hypopharyngeal gland size	1	
	Encapsulation rate	1	
	APISMIN gene expression	4 (3)	
	PKA-R1 (detoxification gene)	1	
	Total	33 (32)	

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129 **Table S2. The mean and maximum concentrations of agrochemicals found in the pollen and nectar of**

130 **crops and plants and in the nectar and pollen content found in bee colonies** [12–15]

Agrochemical	Agrochemical Type	Mean (ppb)	Maximum (ppb)	Reference
Acetamiprid	Neonicotinoid	12.266	112.8	[12]
Chlorantraniliprole	Ryanoid	659.5	2600	[13]
Chlorpyrifos	Organophosphate	18.25	830	[12]
Clothianidin	Neonicotinoid	6.61	319	[12,14]
Coumaphos	Phosphorothioate	105.5	5917	[12]
Cyprodinil	Fungicide	13.2	344	[12]
Deltamethrin	Pyrethroid	4 .6	91	[12]
Diflubenzuron	Benzoylurea	79.7	128	[12]
Fipronil	Phenylpyrazole	33.6	70	[14]
Flumethrin	Pyrethroid	6.7	158	[12]
Flusilazole	Fungicide	14.6	71	[12]
Flupyradifurone	Butenolide	113.6	1800	[15]

Agrochemical	Agrochemical Type	Mean (ppb)	Maximum (ppb)	Reference
Imazalil	Fungicide	1	1	[12]
Imidacloprid	Neonicotinoid	8.43	912	[12,14]
Iprodione	Fungicide	3.5	10	[12]
Lambda-cyhalothrin	Pyrethroid	3.9	36.2	[12]
Methoxyfenozide	Carbohydrazide	2.9	128	[12]
Picoxystrobin	Fungicide	15	15	[16]
Propiconazole	Fungicide	5.5	361	[12]
Pyraclostrobin	Fungicide	25.5	265	[12]
Tau-fluvalinate	Pyrethroid (synthetic)	15.9	2670.0	[12]
Thiacloprid	Neonicotinoid	41.86	187.6	[12,14]
Thiamethoxam	Neonicotinoid	9.584	162.1	[12,14]

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134 **Table S3. The mean and maximum concentrations of agrochemical residue (ppb) found in the nectar**

135 **and pollen of flowers/crops as well as the nectar found in bee colonies.** Field realistic acute exposure for

136 both honeybees and bumblebees were worked out using the mean amount of nectar ingested while a bee

137 foraged.

Agrochemical	Agrochemical Type	Mean (ppb)	Maximum (ppb)	Honeybee mean (ng/40mg)	Honeybee maximum (ng/40mg)	Bumble bee mean (ng/37.7mg)	Bumble bee maximum (ng/37.7mg)
Acetamiprid	Neonicotinoid	2.4	2.4	0.096	0.096	0.090	0.090
Chlorantraniliprole	Ryanoid	659.5	2600	263.8	1,040	248.63	980.2
Clothianidin	Neonicotinoid	7.765	319	0.310	12.76	0.292	12.026
Chlorpyrifos	Organophosphate	3.9	15	0.156	0.6	0.147	0.565
Coumaphos	Phosphorothioate	105.5	2020	4.22	80.8	3.977	76.154
Cyprodinil	Fungicide	13.2	344	0.52	13.76	0.49	12.96
Deltamethrin	Pyrethroid	4.6	6.7	0.184	0.268	0.173	0.252
Diflubenzuron	Benzoylurea	79.7	128	31.88	51.2	30.04	48.25
Fipronil	Phenylpyrazole	33.6	100	1.344	4.0	1.266	3.77
Flumethrin	Pyrethroid	6.7	158	0.268	6.32	0.252	5.956
Flusilazole	Fungicide	14.6	71	0.584	2.84	0.55	2.67
Flupyradifurone	Butenolide	131.5	1500	5.26	60	4.95	56.55
Imazalil	Fungicide	1	1	0.04	0.04	0.037	0.037
Imidacloprid	Neonicotinoid	5.226	95.2	0.209	3.808	0.197	3.589

Iprodione	Fungicide	3.5	10	1.4	4	1.31	3.77
Lambda-cyhalothrin	Pyrethroid	3.9	36.2	0.156	1.448	0.147	1.364
Methoxyfenozide	Carbohydrazide	2.9	128	1.16	51.2	1.09	48.25
Propiconazole	Fungicide	5.5	361	0.22	14.44	0.207	13.60
Pyraclostrobin	Fungicide	25.5	265	1.02	10.6	0.96	9.99
Tau-fluvalinate	Pyrethroid (synthetic)	15.9	750	0.636	30	0.599	28.275
Thiacloprid	Neonicotinoid	4.15	6.5	0.166	0.26	0.156	0.245
Thiamethoxam	Neonicotinoid	4.054	20	0.162	0.8	0.152	0.754

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147 **Table S4. In tank concentration of agrochemicals used in spray treatment**

Agrochemical	Agrochemical Type	Mean concentration of active substance	Maximum concentration of active substance	Reference
Acetamiprid	Neonicotinoid	200 g/kg	200 g/kg	[17]
Azoxystrobin	Fungicide	250g/L	250g/L	[18]
Cypermethrin	Pyrethroid	500g/L	500g/L	[19]
Cyprodinil	Fungicide	625 g/kg	75 g/kg	[20]
Deltamethrin	Pyrethroid	25g/L	50g/L	[21]
Flusilazole	Fungicide	250g/L	250g/L	[22]
Glyphosate	Herbicide	360g/L	360g/L	[23]
Imidacloprid	Neonicotinoid	700g/kg	700g/kg	[24]
Lambda-cyhalothrin	Pyrethroid	100g/L	100g/L	[25]
Mancozeb	Fungicide	750g/kg	750g/kg	[26]

Agrochemical	Agrochemical Type	Mean concentration of active substance	Maximum concentration of active substance	Reference
Oxamyl	Carbamate pesticide	100g/L	100g/L	[27]
Picoxystrobin	Fungicide	241g/L	250g/L	[16]
Prochloraz	Fungicide	450g/L	450g/L	[28]
Propiconazole	Fungicide	250 g/L	250 g/L	[29]
Pyraclostrobin	Fungicide	101.38g/kg	250g/kg	[30]
Sulfoxaflor	Sulfoximine	120g/L	120g/L	[31]
Spinetoram	Spinosad	250 g/kg	250 g/kg	[32]
Tebuconazole	Fungicide	204g/L	250g/L	[33]
Tetraconazole	Fungicide	40g/L	40g/L	[34]
Thiacloprid	Neonicotinoid	320g/kg	400g/kg	[35]
Tolylfluanid	Fungicide	450g/L	450g/L	[36]

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152   of data points remaining following the removal of 29 effect sizes where it was not possible to determine
153   the interaction type (see methods: statistical analysis).

Treatments evaluated	Dependent variable category				
	Mortality	Fitness	Behaviour	Pathogen	Immune
Agrochemicals					
Neonicotinoids					
Acetamiprid	7	0	2	0	0
Clothianidin	19	7	10 (9)	2	2
Flupyradifurone	8	0	6	0	4 (3)
Imidacloprid	23 (21)	11 (10)	27 (26)	1	14
Thiacloprid	16 (15)	0	6	3	3
Thiamethoxam	25 (21)	8 (7)	10	0	1
mixed neonicotinoids (Thiamethoxam and Clothianidin)	2	2	1	1	0
mixed pesticide (Thiamethoxam + Tau-flavinate)	2	0	0	0	0
Pyrethroids					
Bifenthrin	3	0	0	0	0
λ-cyhalothrin	2 (1)	2	2	0	2
Cypermethrin	3	0	3 (2)	0	0
Deltamethrin	9	0	0	0	0
Other agrochemical classes					
Acetic acid	0	0	0	1	0
Amitraz	2	0	0	0	0
Apistan	0	1 (0)	0	1 (0)	0
Bracket97 [acephate]	0	1	2	0	2
Break-through (adjuvicant)	1	1	0	0	0

Treatments evaluated	Dependent variable category				
	Mortality	Fitness	Behaviour	Pathogen	Immune
Chlorantraniliprole	2	0	0	0	0
Chlorpyrifos	0	2	0	0	0
Coumaphos	0	0	4	0	0
Cr (heavy metal used in pesticides)	2	0	0	0	0
Diflubenzuron	2	0	0	0	0
Dimethoate	0	0	0	0	1
Fipronil	14	1	6	6	0
Fluvalinate	0	0	0	0	1
Formic acid	0	0	0	1	0
Methoxyfenozide	2	0	0	0	0
N-90	0	1	1	0	0
Nicotine	0	0	0	1	0
Oxamyl	1	2	2	0	2
Pristine	1	2	3	0	0
Propiconazole	1	0	0	0	0
Spinetoram	3	0	0	0	0
Sulfoxaflor	1	1	2	0	2
Sylgard 309	1	0	0	1	1
Terramycin	0	1 (0)	0	1 (0)	0
Thymol	0	0	1 (0)	1	0
Fungicides					
Azoxystrobin	1	0	0	0	0
Cyprodinil	1	0	0	0	0
Difenoconazole	2	0	0	0	0
Fenhexamid	2	0	0	0	0
Flusilazole	2	0	0	0	0

Treatments evaluated	Dependent variable category				
	Mortality	Fitness	Behaviour	Pathogen	Immune
Imazalil	8	0	6 (5)	0	0
Iprodione	3	0	0	0	0
Mancozeb	1	0	0	0	0
Myclobutanil	4	0	2	0	0
Picoxystrobin	1 (0)	0	0	0	0
Prochloraz	10	0	0	1	1
Propiconazole	17	1	6	0	0
Pyraclostrobin	1	0	0	0	0
Pyraclostrobin + Boscalid	2	0	0	0	0
Rovral-4F	0	0	2	0	0
Tebuconazole	1 (0)	0	0	0	0
Tetraconazole	1	2	2	0	2
Tolylfluanid	1	0	0	0	0
Herbicides					
Paraquat	3	0	0	3	0
Glyphosate	1	2	5	0	2
Parasites					
Fungi					
Ascosphaera aggregata	4	0	0	0	0
Ascosphaera apis	6	0	0	0	0
Ascosphaera atra	1	0	0	0	0
Ascosphaera larvis	4	0	0	0	0
Ascosphaera proliperda	1	0	0	0	0
Aspergillus flavus	3	0	0	0	0
Aspergillus fumigatus	3	0	0	0	0
Aspergillus phoenicis	3	0	0	0	0
Bacteria					

Treatments evaluated	Dependent variable category				
	Mortality	Fitness	Behaviour	Pathogen	Immune
Bacillus thuringiensis	4	0	0	0	0
Bacterial immune challenge	2	0	0	0	0
Bacterial solution (*Arthrobacter globiformis* and *Escherichia coli*)	0	1 (0)	0	0	0
Enterococcus faecalis	4	0	4	0	3
Escherichia coli	1 (0)	0	0	0	0
Paenibacillus larvae (American foulbrood)	7 (5)	2	2	0	3
Snodgrassella alvi	0	0	0	2	0
Microsporidia					
Nosema apis	4 (1)	0	2	7	0
Nosema bombi	0	0	1 (0)	0	0
Nosema ceranae	35 (26)	2	13	22	9 (8)
Nosema sp	8	2	3	1	2
Trypanasomes					
Lotmaria passim	0	0	0	3	0
Crithidia bombi	5 (4)	5	3	1	1
other protozoan parasites					
Apicystis	1	1	0	0	0
Viruses					
ABPV	1	0	0	0	0
APV	5 (3)	0	0	0	0
BQCV	8	2	2	4	0
CBPV	4	0	2	0	0
CPV	1	0	1	0	0
DWV (various strains)	4 (2)	1	0	3	1
Flock house virus	2	0	0	0	0
Israeli acute paralysis virus	1	0	1	2	1

Treatments evaluated	Dependent variable category				
	Mortality	Fitness	Behaviour	Pathogen	Immune
LSV	0	0	0	1	0
SBPV	1	0	0	0	0
unnamed invertebrate iridescent virus (IIV)	1	0	0	0	0
Multicellular parasites					
Varroa mite	4 (3)	4	5	0	1
Acarapis woodi	2 (1)	3	1	0	0
Tropilaelaps clarae	0	0	1	0	0
Nutrition					
Bee bread (+/-)	4	1	0	3	0
Pollen deprivation	5 (1)	1	1	2	5
Reduced royal jelly and/or sugar	9	0	0	0	0
Pollen (high/low quantity)	1	0	0	0	0
Pollen diet quality	7 (5)	8 (6)	3	0	0
Quantity of pollen received as larvae	0	1	0	0	0
Quantity of pollen received as adult	0	1	0	0	0
Starvation	1	0	0	0	0
Sucrose concentration	13	0	2	1	0
Supplemental protein (+/-)	0	1	0	0	0
Supplemental sugar (+/-)	0	2 (1)	0	0	0

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Table S6: Results from sensitivity analysis on non-independence within samples. Note that the table above ICCA = an ICC of 0.26 and ICCB = an ICC of 0.76

Original results	PE	CI	CI
Parasite-Parasite	0.04	-0.16	0.24
Parasite-Agrochemical	0.1	-0.06	0.26
Parasite-Nutrition	-0.12	-0.42	0.17
Agrochemical-Agrochemical	0.32	0.13	0.52
Agrochemical-Nutrition	0.25	-0.008	0.51
Nutrition-Nutrition	-0.51	-0.83	-0.18
Overall	0.18	0.08	0.28
Results ICCA	**PE**	**CI**	**CI**
Parasite-Parasite	0.04	-0.16	0.25
Parasite-Agrochemical	0.12	-0.04	0.3
Parasite-Nutrition	-0.03	-0.25	0.17
Agrochemical-Agrochemical	0.31	0.12	0.49
Agrochemical-Nutrition	0.24	-0.003	0.49
Nutrition-Nutrition	-0.51	-0.83	-0.18
Overall	0.18	0.08	0.28
Results ICCB	**PE**	**CI**	**CI**
Parasite-Parasite	0.03	-0.18	0.26
Parasite-Agrochemical	0.07	-0.1	0.26
Parasite-Nutrition	-0.01	-0.21	0.19
Agrochemical-Agrochemical	0.31	0.12	0.5
Agrochemical-Nutrition	0.21	0.02	0.44
Nutrition-Nutrition	-0.51	-0.83	-0.18
Overall	0.16	0.06	0.26

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