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Assessment of occupational exposure to pesticide mixtures with endocrine disrupting activity

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Supplementary Material

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Table S1 Classification of 48 pesticide active substances with known or possible endocrine activity by pesticide type, chemical group, and approval status in the EU. All information sourced from the Pesticide Properties Database (PPDB 2018)

Table S2 List of pesticide co-formulants used in the UK orchard system that were identified as having potential endocrine activity based on the Hazardous Substances Data Bank (HSDB) of the TOXNET database and the Pesticide Properties Database (PPDB 2018)

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Table S4 Summary of toxicological data for 48 active substances with known or possible endocrine activity

Figure legend

Fig. S1 Comparison of relative contributions of fungicides, insecticides and herbicides to the total use (a), total exposure (b) and total risk (c) associated with known/possible endocrine disrupting activity across the five cropping systems over the survey period

References

Table S1 Classification of 48 pesticide active substances with known or possible endocrine activity by pesticide type, chemical group, and approval status in the EU. All information sourced from the Pesticide Properties Database (PPDB 2018)

Active substances	Pesticide type	Substance group	Endocrine disrupting classification	Status of use
2,4-D	Herbicide	Alkylchlorophenoxy	Possibly	Approved
Amitrole	Herbicide	Triazole	Possibly	Not approved
Beta-cyfluthrin	Insecticide	Pyrethroid	Possibly	Approved
Bifenthrin	Insecticide	Pyrethroid	Yes	Approved
Bromoxynil	Herbicide	Hydroxybenzonitrile	Yes	Approved
Bupirimate	Fungicide	Pyrimidinol	Possibly	Approved
Captan	Fungicide	Phthalimide	Possibly	Approved
Carbendazim	Fungicide	Benzimidazole	Possibly	Not approved
Chlorothalonil	Fungicide	Chloronitrile	Possibly	Approved
Chlorpyrifos	Insecticide	Organophosphate	Possibly	Approved
Chlorpyrifos-methyl	Insecticide	Organophosphate	Possibly	Approved
Copper oxychloride	Fungicide	Inorganic compound	Possibly	Approved
Cypermethrin (alpha-/zeta-cypermethrin)	Insecticide	Pyrethroid	Possibly	Approved
Cyproconazole	Fungicide	Triazole	Possibly	Approved
Deltamethrin	Insecticide	Pyrethroid	Yes	Approved
Difenoconazole	Fungicide	Triazole	Possibly (based on open literature)[a]	Approved
Epoxiconazole	Fungicide	Triazole	Possibly	Approved
Esfenvalerate	Insecticide	Pyrethroid	Possibly	Approved
Fenbuconazole	Fungicide	Triazole	Possibly	Approved
Fenoxycarb	Insecticide	Carbamate	Yes	Approved

Fluazinam	Fungicide	Phenylpyridinamine	Possibly	Approved
Flusilazole	Fungicide	Triazole	Possibly	Not approved
Glyphosate	Herbicide	Phosphonoglycine	Possibly	Approved
Indoxacarb	Insecticide	Oxadiazine	Possibly	Approved
Ioxynil	Herbicide	Hydroxybenzonitrile	Yes	Not approved
Linuron	Herbicide	Urea	Possibly	Approved
Mancozeb	Fungicide	Carbamate	Possibly	Approved
Maneb	Fungicide	Carbamate	Possibly	Approved
Metconazole	Fungicide	Triazole	Possibly	Approved
			(based on open literature)[b]	
Methoxyfenozide	Insecticide	Diacylhydrazine	Possibly	Approved
Metiram	Fungicide	Carbamate	Possibly	Approved
Metribuzin	Herbicide	Triazinone	Possibly	Approved
Myclobutanil	Fungicide	Triazole	Possibly	Approved
Paclobutrazol	Fungicide	Triazole	Possibly	Approved
			(based on open literature)[c]	
Penconazole	Fungicide	Triazole	Possibly	Approved
Pendimethalin	Herbicide	Dinitroaniline	Possibly	Approved
Picloram	Herbicide	Pyridine compound	Yes	Approved
Prochloraz	Fungicide	Imidazole	Possibly	Approved
Propamocarb (hydrochloride)	Fungicide	Carbamate	Possibly	Approved
Propiconazole	Fungicide	Triazole	Possibly	Approved
Pyrimethanil	Fungicide	Anilinopyrimidine	Possibly	Approved
Pyriproxyfen	Insecticide	Unclassified	Possibly	Approved
S-metolachlor	Herbicide	Chloroacetamide	Possibly	Approved
Tau-fluvalinate	Insecticide	Synthetic pyrethroid	Yes	Approved

Tebuconazole	Fungicide	Triazole	Possibly (based on open literature)[d]	Approved
Triadimenol	Fungicide	Triazole	Yes	Approved
Tribenuron-methyl	Herbicide	Sulfonylurea	Possibly	Approved
Ziram	Fungicide	Carbamate	Possibly	Approved

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Table S2 List of pesticide co-formulants used in the UK orchard system that were identified as having potential endocrine activity based on the Hazardous Substances Data Bank (HSDB) of the TOXNET database and the Pesticide Property Database (PPDB 2018)

Chemical name	CAS No.	Potential ED effect(s)
1-methoxy-2-propanol	107-98-2	Mild damage to the liver and adrenal glands were observed in laboratory rats following repeated exposure to high vapour levels.
1,2-propanediol/propane-1,2-diol/propylene glycol	57-55-6	Seizures developed in an 11-year old boy with multiple endocrine problems and systemic candidiasis who ingested a medication containing propylene glycol. Endocrine modulation: did not cause any significant changes in adrenal steroidogenesis in the rat; spleen weights were increased in the treatment groups in acute exposure.
1,2,4-trimethylbenzene	95-63-6	Rat (4-week): observations in high dose group (2.0g/kg) included enlarged adrenals (only 2 doses tested; low dose: 0.5 g/kg diet).
2-ethylhexan-1-ol	104-76-7	Rat (11-day): absolute spleen weights of both sexes were reduced at 1000 mg/kg bw/d; decreased absolute spleen and adrenal weights at 1500 mg/kg bw/d.
3-pyridinecarboxamide, 2-chloro-N-(4'-chloro(1,1'-biphenyl)2-yl)-	188425-85-6	Induction of liver microsomal enzyme system resulting in increased glucuronidation of thyroxine, resulting in an increase in TSH secretion as a compensatory response of the physiological negative feedback system; increased TSH resulted in increased thyroid weight.
4,4'-methylenediphenyl diisocyanate/diphenylmethane-4,4'-diisocyanat	101-68-8	Repeated doses for 5 days in corn oil produced slight spleen enlargement in rats.
Amines, tallow alkyl, ethoxylated/polyetoxylated N-tallow alkyltrimethylenedi-amine/tallowalkylamineethoxylate	61791-26-2	Polyethoxylated tallow amine: decrease of aromatase activity, a key enzyme in the balance of sex hormones (Defarge et al. 2016).

Ammonium sulphate/sulfate	7783-20-2	Rat (1-year): absolute spleen weights were decreased in high dose males.
Citric acid	77-92-9	Rat (6-week): slight degeneration of the thymus gland and spleen.
Cumene	98-82-8	Rat (2-week inhalation): For females in the two highest dose groups, the relative and absolute adrenal weights were increased significantly over control values.
Ethylene glycol	107-21-1	Target organ cellular damage is seen in the kidney, brain, myocardium, pancreas, and blood vessel walls.
Hydrocarbon, C9, aromatics	N/A	Polycyclic aromatic hydrocarbons (PAHs):
Hydrocarbon, C10, aromatics, <1% naphthalene	N/A	Endocrine modulation: PAHs exhibited either weakly estrogenic or antiestrogenic
Hydrocarbons, C11-C14, n-alkanes, isoalkanes, cyclics <2% aromatic	N/A	responses.
Lignin, alkali, reaction products with sodium bisulfite and formaldehyde/Lignosulfonic acid, sodium salt/sodium ligninsulfonate	8061-51-6	When given to rats in drinking-water 16-week; spleen changes.
Naphtha/petroleum distillates	64742-94-5	Rat (7/8-week developmental/reproductive toxicity, f/m): increased spleen weights in parental females at 7500 ppm.
Naphthalene	91-20-3	Mice (14- and 90-day): Females had decreased spleen at the high dose, 267 mg/kg and 133 mg/kg, respectively. Mice (14- and 90-day): Females had decreased spleen at the high dose, 267 mg/kg and 133 mg/kg, respectively.
N-methyl-2-pyrrolidone/methyl pyrrolidone	872-50-4	Subchronic exposure of rats had atrophy of lymphoid tissue in the spleen and thymus.
Nonylphenol ethoxylated/polyethylene glycol nonylphenyl ether	9016-45-9	Nonylphenol: discovered to have estrogenic activity.
Talc	14807-96-6	There was clear evidence of carcinogenic activity of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or

		malignant pheochromocytomas of the adrenal gland.
Cyprodinil	121552-61-2	Cyprodinil acts as an aryl hydrocarbon receptor activator, a potential endocrine disrupter, and an extracellular signal-regulated kinase disrupter. Weak androgen receptor binding was shown for cyprodinil.
Dicamba	1918-00-9	Rat (115-118 weeks): adrenal enlargement was increased at >/= 250 ppm in both sexes.
Diquat (diquat dibromide)	2764-72-9	Diquat dibromide (1-year): reductions in adrenal and epididymal weights were noted in males.
Fludioxonil	131341-86-1	Endocrine modulation: fludioxonil showed endocrine disruptor activity as antiandrogens in an androgen receptor reporter assay in engineered human breast cancer cells.
Fumaric acid	110-17-8	Rabbit (17-29 weeks): by the end of the test period, gonadotropic activity of the serum, as well as estrogenic activity was detected. Chromophobe cells were increased in the pituitary.
Metribuzin	21087-64-9	Metribuzin shows effects in single high doses corresponding to a depression of the CNS system. With repeated high doses, it effects the thyroid and stimulates the metabolizing enzymes of the liver.
Pyraclostrobin	175013-18-0	Subchronic or prechronic exposure/ Mice, in a 90-day feeding study, also showed thickening of the duodenal mucosa together with erosion or ulcers in the glandular stomach and a decrease in lipid vacuolization in the adrenal cortex. Females were more sensitive than males with adrenal effects occurring at 50 ppm (12.9 mg/kg/day).

Table S3 Equations to predict median exposure to pesticides on a daily basis; the total amount of active substance/co-formulant (TA) is the major parameter for exposure; the slope α was set to 1 in case α >1; exposure is given in µg/person (Groβkopf et al. 2013)

Tank ML	$\log exposure = \alpha \cdot \log TA + [formulation\ type] + constant$
Total hands	$\log DE_{ML(H)} = 0.71 \cdot \log TA + 0.57\ [liquid] + 1.55\ [WP] - 0.34\ [glove\ wash] + 2.73$
Protected hands	$\log DE_{ML(Hp)} = 0.39 \cdot \log TA + 0.17\ [liquid] + 1.74\ [WP] + 1.02$
Total body	$\log DE_{ML(B)} = 0.71 \cdot \log TA + 0.24\ [liquid] + 1.69\ [WP] + 2.87$
Protected body	$\log DE_{ML(Bp)} = 0.95 \cdot \log TA - 0.05\ [liquid] + 1.99\ [WP] + 0.87$
Head	$\log DE_{ML(C)} = \log TA + 0.55\ [liquid] + 1.31\ [WP] + 1.52\ [no\ face\ shield] - 1.07$
Inhalation	$\log IE_{ML} = 0.53 \cdot \log TA - 0.73\ [liquid] + 2.26\ [WP] + 0.61$
LCTM AP[a]	$\log exposure = \alpha \cdot \log TA + [droplet] + [equipment] + constant$
Total hands	$\log DE_{AP(H)} = \log TA + 1.43\ [normal\ droplet] - 1.41\ [normal\ equipment] + 1.30$
Protected hands	$\log DE_{AP(Hp)} = \log TA + 1.46\ [normal\ droplet] - 0.61\ [normal\ equipment] - 0.67$
Total body	$\log DE_{AP(B)} = \log TA + 0.56\ [normal\ droplet] - 1.62\ [normal\ equipment] + 2.52$
Protected body	$\log DE_{AP(Bp)} = log\ TA + 0.34\ [normal\ droplet] - 0.94\ [normal\ equipment] + 0.49$
Head	$\log DE_{AP(C)} = \log TA + 0.32\ [normal\ droplet] - 0.22\ [normal\ equipment] - 0.22$
Inhalation	$\log IE_{AP} = 0.46 \cdot \log TA + 0.13\ [normal\ droplet] + 0.65\ [normal\ equipment] - 0.89$
HCTM AP	$\log exposure = \alpha \cdot \log TA + [cabin] + constant$
Total hands	$\log DE_{AP(H)} = 0.49 \cdot \log TA + 0.89\ [no\ cabin] + 2.29$
Protected hands	$\log DE_{AP(Hp)} = 0.88 \cdot \log TA + 1.18$[c]
Total body	$\log DE_{AP(B)} = \log TA + 0.86\ [no\ cabin] + 2.86$
Protected body	$\log DE_{AP(Bp)} = \log TA + 0.50\ [no\ cabin] + 1.30$
Head	$\log DE_{AP(C)} = \log TA + 1.46\ [no\ cabin] + 0.82$
Inhalation	$\log IE_{AP} = 0.63 \cdot \log TA + 1.00\ [no\ cabin] + 0.51$
HCHH AP[b]	$\log exposure = \alpha \cdot \log TA + [culture] + constant$
Total hands	$\log DE_{AP(H)} = \log TA - 0.94\ [normal\ culture] + 4.02$
Protected hands	$\log DE_{AP(Hp)} = \log TA - 1.26\ [normal\ culture] + 1.90$
Total body	$\log DE_{AP(B)} = 0.32 \cdot \log TA - 1.50\ [normal\ culture] + 5.75$
Protected body	$\log DE_{AP(Bp)} = \log TA - 1.48\ [normal\ culture] + 3.72$
Head	$\log DE_{AP(C)} = 0.34 \cdot \log TA - 1.18\ [normal\ culture] + 2.87$
Inhalation	$\log IE_{AP} = 0.74 \cdot \log TA - 0.57\ [normal\ culture] + 2.13$

[a] For LCTM AP, the droplet sizes are grouped into 'normal' and 'coarse' subsets with the latter size being chosen when drift reducing nozzles are used; the 'normal' and 'small' equipment subsets are used with the small equipment for treatment in small areas/high crops.

[b] For HCHH AP, the 'normal' and 'dense' culture subsets with the dense culture refers to unavoidable direct contact with sprayed crop during applications.

[c] The dependency of the factor [cabin] was not significant.

AP, application; ML, mixing/loading; DE, dermal exposure; IE, inhalation exposure; H, total hands; Hp: protected hands; B, total body; Bp, protected body; C, head; WP, wettable powder formulation

Table S4 Summary of toxicological data for 48 active substances with known or possible endocrine activity

Active substance	Species / study	Doses	NO(A)EL/LO(A)EL (mg/kg bw/d)	LOAEL / effects	Toxicological database
2,4-D	Rat 90-day oral diet	0, 1, 15, 100, 300 mg/kg/d (average daily compound intake: 0.93, 13.98, 93.93, 278.39 mg/kg/d for males and 0.96, 14.39, 96.16, 293.42 mg/kg/d for females)	NOAEL: 15	LOAEL: 100 mg/kg/d based on the alterations in some hematology and clinical chemistry (decreased T_3 (females) and T_4 (both sexes)) parameters, and cataract formation in females.	EPA (EDSP Tier 1)
Amitrole	Rat 90-day oral	0, 2, 10, 50 ppm (0.11, 0.58, 2.85 mg/kg bw/d)	NOAEL: 0.11 (2 ppm)	LOAEL: 10 ppm equivalent to 0.58 mg/kg bw/d based on the thyroid effect.	EFSA (DAR)
Beta-cyfluthrin (cyfluthrin)	Rat 4-week gavage (once daily)	0, 5, 20, 80 mg/kg bw/d	NOEL: 20	Increased absolute and relative weights of the adrenal glands in female rats at the end of treatment at the highest dose.	TOXNET (HSDB)
Bifenthrin	Rat 28-day	0, 50, 100, 200, 300, 400 ppm (approximately 0, 4.4, 10.75, 21.9 and 34.5 mg/kg bw/d in males and 0, 5.4, 11, 21.6 and 32.6 mg/kg bw/d in females)	NOAEL: 21.9 (m) (200 ppm)	Based on significantly elevated adrenal weight and depressed testes weight and relative adrenal in males at 300 ppm group.	IPCS INCHEM (JMPR); ECHA (2009)
Bromoxynil	Dog 13-week oral (7 days/week)	0, 0.43, 1.43, 7.14 mg/kg/d	NOEL: <0.43	Increased absolute and relative adrenal weights.	TOXNET (HSDB)

Bupirimate	Dog 90-day oral diet	0, 3, 15, 30, 600 mg/kg bw/d	NOAEL: 3	LOAEL: 15 mg/kg bw/d based on Increased thyroid weight.	EFSA (DAR)
Captan	Rat 2-year	0, 25, 100, 250 mg/kg/d	NOEL: 25	Increased relative organ weights of liver and thyroid/parathyroid (F) and kidney (m & f).	TOXNET (HSDB)
Carbendazim	Dog 13-week diet	0, 100, 300, 1000 ppm	NOAEL: 7.5 (300 ppm)	On the basis of minor changes in clinical chemistry and organ weights. There were slight increases in relative thyroid weight in the group at the highest dose.	IPCS INCHEM (JMPR)
Chlorothalonil	Dog 1-year	0, 160, 1280, 10240 ppm (0, 5.10, 43.26, 374 mg/kg/d in males and 0, 5.92, 45.30, 354 mg/kg/d in females)	NOAEL: 43.3/45.3 (m/f) (1280 ppm)	LOAEL: 10240 ppm based on a very slight hypertrophy of the cells in the zona fasciculate of the adrenal glands.	EPA (EDSP Tier 1)
Chlorpyrifos	Rat 13-week	-	NOAEL: 5	Increased fatty vacuolation of the adrenal zonal fasciculate and changes in haematological and clinical chemical parameters.	IPCS INCHEM (JMPR)
Chlorpyrifos-methyl	Rat 13-week	0, 0.1, 1, 10, 250 mg/kg bw/d	NOAEL: 1	On the basis of histological alterations detected in adrenals at 10 mg/kg bw/d.	IPCS INCHEM (JMPR)
Copper oxychloride (copper)	Rat 15-day	0, 1000, 2000, 4000, 8000, 16000 ppm (23, 44, 162, 196, 285 mg/kg bw/d in males and 23, 46, 92, 198, 324 mg/kg bw/d in females	NOAEL: 23 (1000 ppm)	A minimal to mild decrease in erythroid haematopoesis was seen in the spleens at ≥ 2000 ppm. (No guideline GLP with deviations of 15-day instead of 28-day).	ECHA (2013)

Cypermethrin (alpha-cypermethrin/zeta-cypermethrin)	Rat 15-day oral gavage	0, 6.25, 12.5, 25, 50 mg/kg/d	NOEL: 6.25	Damage to the seminiferous tubules and spermatids in studies reported as other scientifically relevant information (OSROI) (Hu et al. 2011)	EPA (EDSP Tier 1)
Cyproconazole	Rat 90-day	5, 15, 300, 600 ppm (0.7, 2.2, 43.8, 88.8 mg/kg bw/d in males and 1.0, 3.2, 70.2, 128.2 mg/kg bw/d in females)	NOAEL: 0.7/1.0 (m/f) (5 ppm)	Increased relative adrenal weight in females at 15 ppm (2.2/3.2 mg/kg bw/d).	ECHA (2014)
Deltamethrin	Rat 65-day	1, 2 mg/kg w/d	LOEL: 1 (divided by 1000-factor for NOEL: 0.001)	Based on spermatogenesis, testosterone levels and pituitary weight *in vivo*.	EC (EDS)
Difenoconazole	Dog 6-month diet	0, 100, 1000, 3000, 6000 ppm (0, 3.6, 31.3, 96.6, 157.8 mg/kg/d in males and 0, 3.4, 34.8, 110.6, 203.7 mg/kg/d in females)	NOAEL: 31.3/34.8 (m/f) (1000 ppm)	Based on decreased prostate weight.	EFSA (DAR)
Epoxiconazole	Rat 13-week dietary	30, 90, 270, 800 ppm	NOAEL: 7/8 (m/f) (90 ppm)	Both absolute and relative adrenal weights were slightly reduced in all treated groups, but more clearly so at the upper two dose levels.	EFSA (DAR)
Esfenvalerate	Rat 90-day diet	0, 50, 150, 300 or 500 ppm	NOAEL: 7.5 (150 ppm)	On the basis of parenchymal-cell hypertrophy in the parotid salivary and pituitary glands in some rats at 300 ppm.	IPCS INCHEM (JMPR)
Fenbuconazole	Rat 3-month dietary	0, 20, 80, 400, 1600 ppm	NOAEL: 1.3 (20 ppm)	Hypertrophy of thyroid gland follicular cells at higher doses.	IPCS INCHEM (JMPR)

Fenoxycarb	Rat 3-month oral	0, 30, 150, 750, 3000 ppm	NOEL: 9.71/10.14 (m/f) (150 ppm)	Based on histological changes in thyroid.	TOXNET (HSDB)
Fluazinam	Rat 90-day oral	-	NOAEL: 4.1	LOAEL: 41 mg/kg bw/d. Effect on uterus weight may be indicative of endocrine disruption with no mechanistic evidence.	Ewence et al. (2013)
Flusilazole	Rat 2-year diet	0, 125, 375, or 750 ppm (0, 5.03, 14.8, 30.8 mg/kg bw/d for males and 0, 6.83, 20.5, 45.6 mg/kg bw/d for females)	NOAEL: 14.8	Increased incidence of testicular interstitial-cell (Leydig-cell) tumours in males at the highest dose.	IPCS INCHEM (JMPR)
Glyphosate	Dog 13-week oral	0, 30, 300, 1000 mg/kg bw/d	NOAEL: 300	LOAEL: 1000 mg/kg bw/d based on prostate and uterus atrophy.	ECHA (2016)
Indoxacarb	Rat 90-day	0, 10, 25 (females only), 50, 100, 200 (males only) (0, 0.62, 3.09, 6.01, 15 mg/kg/d for males and 0, 0.76, 2.13, 3.78, 8.94 mg/kg/d for females)	NOEL: 0.62/<0.76 (m/f) (10 ppm)	Histologic effects in the spleen.	TOXNET (HSDB)
Ioxynil	Rat 90-day oral	-	NOEL: 0.7 to 1.4	LOAEL: 10 mg/kg bw/d. There appears to be an increase in basal metabolism and an effect on the thyroid.	Ewence et al. (2013)
Linuron	Rat 2-year	-	NOEL: 6.25 (125 ppm)	Spleen and bone marrow changes indicative of haemolysis, increased mortality, growth retardation.	IRIS
Mancozeb	Rat 13-week oral	0, 30, 60, 125, 250, 1000 ppm	NOAEL: 7.4 (125 ppm)	Increased serum TSH and decreased T4 values at 250 ppm.	IPCS INCHEM (JMPR)

Maneb	Dog 13-week dietary	0, 100, 400, 1600 ppm	NOAEL: 3.7 (100 ppm)	Based on thyroid follicular cell hyperplasia at 400 ppm.	IPCS INCHEM (JMPR)
Metconazole	Mouse 90-day oral	0, 30, 300, 2000 ppm	NOAEL: 4.6 (30 ppm)	LOAEL: 50.5 mg/kg/d (300 ppm) based on increased spleen weight and spleen lymphoid hyperplasia.	EFSA (DAR)
Methoxyfenozide	Rat 2-week diet	250, 1000, 5000, 20000 mg/kg diet	NOAEL: 24 (250 mg/kg diet)	On the basis of follicular cell hypertrophy and/or hyperplasia of the thyroid in both sexes at 1000 mg/kg (equal to 98 mg/kg bw/d).	IPCS INCHEM (JMPR)
Metiram	Rat 13-week dietary	0, 50, 100, 300, 900 (equal to 0, 3, 6, 20, 61 mg/kg bw/d for males and 0, 4, 8, 24, 76 mg/kg bw/d for females)	NOAEL: 6 (100 ppm)	Decreased serum T4 levels and increased thyroid weights at dietary levels of 300 and 900 ppm.	IPCS INCHEM (JMPR)
Metribuzin	Rat 9-week oral	0, 35, 100, 300, 900 ppm	NOAEL: ≤ 2.41 (≤ 35 ppm)	LOAEL: ≥ 35 ppm: effects on thyroid gland and liver.	EFSA (DAR)
Myclobutanil	Rat 13-week diet	0, 100, 300, 3000 ppm (0, 6.2, 18.8, 192 mg/kg bw/d in males and 0, 6.9, 19.6, 225 mg/kg bw/d in females)	NOAEL: 18.8 (300 ppm)	Histomorphological alterations of the liver, kidney and adrenal glands at the highest dietary level of 3000 ppm.	IPCS INCHEM (JMPR)
Paclobutrazol	Dog 1-year	0, 15, 75, 300 mg/kg/d	NOAEL: 75	Based on the slight increase of adrenal weights in females at 300 mg/kg bw/d.	EFSA (DAR)

Penconazole	Rat 28-day gavage	0, 100, 500 mg/kg bw/d	NOAEL: < 100	Thyroids and adrenals (males) with histopathological findings at ≥ 100 mg/kg bw/d.	EFSA (DAR)
Pendimethalin	Rat 90-day oral	-	NOAEL: 41.3	Based on thyroid effects.	EFSA (DAR)
Picloram	Rat 90-day	-	NOEL: 50 (1000 ppm)	LEL: 150 mg/kg/d (3000 ppm) based on liver histopathology, necrosis, and bile duct proliferation.	IRIS
Prochloraz	Dog 13-week gastric intubation	1, 2.5, 7, 20 mg/kg bw/d	NOAEL: 2.5	On the basis of effects on prostate and testes weights at the next highest dose.	IPCS INCHEM (JMPR)
Propamocarb hydrochloride	Rat 2-generation oral reproductive	-	NOAEL: 37.5 (parental & reproductive)	Some evidence of disruption of the male reproductive system (sperm concentration and count).	Ewence et al. (2013)
Propiconazole	Dog 1-year diet (short-term)	0, 50, 250, 1250 ppm	NOAEL: 7 (250 ppm)	Organ weights were not different than those of control animals except for significantly decreased relative pituitary weight in males of the highest dose group.	IPCS INCHEM (JMPR)
Pyrimethanil	Rat 90-day oral	-	NO(A)EL: 5.4	Follicular epithelial hypertrophy and pigment deposits in thyroid.	EFSA (DAR)
Pyriproxyfen	Rat 78-week diet	0, 120, 600, 3000 mg/kg food	NOAEL: 16.4/21.1 (m/f) (120 mg/kg food)	Increased severity of systemic amyloidosis was noted in several organs as the adrenal cortex, thyroid, heart, spleen, kidneys, liver, stomach, ovary, testes, etc.	EFSA (DAR)

S-metolachlor (metolachlor)	Rat Post-natal day 22 to 42 oral gavage	0, 300, 600 mg/kg/d	LO(A)EL: 300 (divided by 1000 for NO(A)EL: 0.3)	Based on a dose-related increase in serum T4 levels of 14% and 25% in the 300 and 600 mg/kg/d groups, respectively; the increase was significant ($p<0.05$) at 600 mg/kg/d only.	EPA (EDSP Tier 1)
Tau-fluvalinate	Dog 6-month	0, 2, 5, 15, 50 mg/kg/d	NOEL: 2	Decreased spleen weight.	TOXNET (HSDB)
Tebuconazole	Rat 90-day feeding	0, 100, 400, 1600 ppm	NOAEL: 9/11 (m/f) (100 ppm)	Histopathological changes (vacuoles) in the adrenal cortex.	EFSA (DAR)
Triadimenol	Mice 13-week	0, 160, 500, 1500, 4500 ppm (0, 25, 77, 235, 872 mg/kg/d in males and 0, 31, 94, 297, 797 mg/kg/d)	NOAEL: 235/297 (m/f) (1500 ppm)	Reduced adrenal weights in the high-dose groups only in males and females.	ECHA (2011)
Tribenuron-methyl	Rat 90-day oral	-	NOAEL: 7/8 (m/f)	LOAEL: 118/135 mg/kg/d (m/f). Increased relative brain, heart, liver, kidney, testes, and spleen weights.	TOXNET (HSDB)
Ziram	Rat 28-day oral	0, 100, 500, 2500, 5000 ppm (0, 10, 50, 250, 500 mg/kg bw/d)	NOAEL: 10 (100 ppm)	On the basis of growth retardation.	IPCS INCHEM (HSDB)

EC (EDS), European Commission Endocrine Disruptors Database; EFSA (DAR), EFSA Draft Risk Assessment Report and Assessment Report; EPA (EDSP Tier 1), EPA Endocrine Disruptor Screening Program Tier 1 screening determinations and associated data evaluation records; IPCS INCHEM (JMPR), Joint Meeting on Pesticide Residues of the International Programme on Chemical Safety; IRIS, Integrated Risk Information System; LO(A)EL, lowest observed (adverse) effect level; NO(A)EL, no observed (adverse) effect level; TOXNET (HSDB), Hazardous Substances Data Bank of Toxicology Data Network

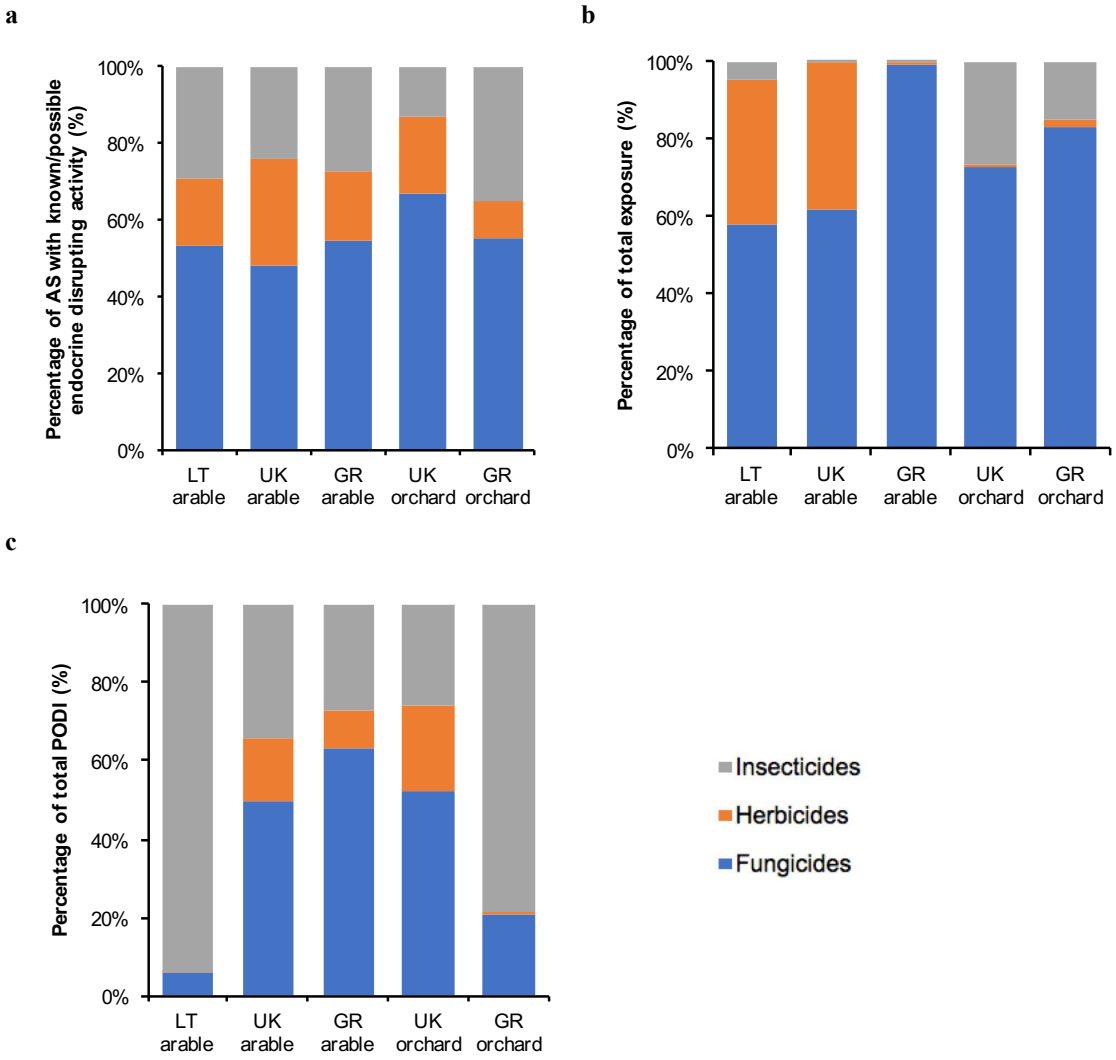

Fig. S1 Comparison of relative contributions of fungicides, insecticides and herbicides to the total use (a), total exposure (b) and total risk (c) associated with known/possible endocrine disrupting activity across the five cropping systems over the survey period

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