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# Assessment of occupational exposure to pesticide mixtures with endocrine disrupting activity

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## Supplementary Material

**Table legend**

**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)

**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)

**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 |

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|---|---|---|---|---|
| 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 |

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|---|---|---|---|---|
| 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 |

[a] Teng M, Qi S, Zhu W, Wang Y, Wang D, Dong K, Wang C (2018) Effects of the bioconcentration and parental transfer of environmentally relevant concentrations of difenoconazole on endocrine disruption in zebrafish (Danio rerio). Environmental Pollution 233:208-217

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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<br>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<br>(EDSP Tier 1) |
| Amitrole | Rat<br>90-day oral | 0, 2, 10, 50 ppm (0.11, 0.58, 2.85 mg/kg bw/d) | NOAEL: 0.11<br>(2 ppm) | LOAEL: 10 ppm equivalent to 0.58 mg/kg bw/d based on the thyroid effect. | EFSA (DAR) |
| Beta-cyfluthrin (cyfluthrin) | Rat<br>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<br>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)<br>(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<br>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<br>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<br>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<br>13-week diet | 0, 100, 300, 1000 ppm | NOAEL: 7.5<br>(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<br>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)<br>(1280 ppm) | LOAEL: 10240 ppm based on a very slight hypertrophy of the cells in the zona fasciculate of the adrenal glands. | EPA<br>(EDSP Tier 1) |
| Chlorpyrifos | Rat<br>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<br>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<br>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<br>(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) |

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|---|---|---|---|---|---|
| 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) |

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|---|---|---|---|---|---|
| Fenoxycarb | Rat<br>3-month oral | 0, 30, 150, 750, 3000 ppm | NOEL: 9.71/10.14 (m/f)<br>(150 ppm) | Based on histological changes in thyroid. | TOXNET (HSDB) |
| Fluazinam | Rat<br>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<br>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<br>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<br>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)<br>(10 ppm) | Histologic effects in the spleen. | TOXNET (HSDB) |
| Ioxynil | Rat<br>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<br>2-year | - | NOEL: 6.25<br>(125 ppm) | Spleen and bone marrow changes indicative of haemolysis, increased mortality, growth retardation. | IRIS |
| Mancozeb | Rat<br>13-week oral | 0, 30, 60, 125, 250, 1000 ppm | NOAEL: 7.4<br>(125 ppm) | Increased serum TSH and decreased T4 values at 250 ppm. | IPCS INCHEM (JMPR) |

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|---|---|---|---|---|---|
| Maneb | Dog<br>13-week dietary | 0, 100, 400, 1600 ppm | NOAEL: 3.7<br>(100 ppm) | Based on thyroid follicular cell hyperplasia at 400 ppm. | IPCS INCHEM (JMPR) |
| Metconazole | Mouse<br>90-day oral | 0, 30, 300, 2000 ppm | NOAEL: 4.6<br>(30 ppm) | LOAEL: 50.5 mg/kg/d (300 ppm) based on increased spleen weight and spleen lymphoid hyperplasia. | EFSA (DAR) |
| Methoxyfenozide | Rat<br>2-week diet | 250, 1000, 5000, 20000 mg/kg diet | NOAEL: 24<br>(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<br>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<br>(100 ppm) | Decreased serum T4 levels and increased thyroid weights at dietary levels of 300 and 900 ppm. | IPCS INCHEM (JMPR) |
| Metribuzin | Rat<br>9-week oral | 0, 35, 100, 300, 900 ppm | NOAEL: ≤ 2.41<br>(≤ 35 ppm) | LOAEL: ≥ 35 ppm: effects on thyroid gland and liver. | EFSA (DAR) |
| Myclobutanil | Rat<br>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<br>(300 ppm) | Histomorphological alterations of the liver, kidney and adrenal glands at the highest dietary level of 3000 ppm. | IPCS INCHEM (JMPR) |
| Paclobutrazol | Dog<br>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) |

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| Penconazole | Rat<br>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<br>90-day oral | - | NOAEL: 41.3 | Based on thyroid effects. | EFSA (DAR) |
| Picloram | Rat<br>90-day | - | NOEL: 50<br>(1000 ppm) | LEL: 150 mg/kg/d (3000 ppm) based on liver histopathology, necrosis, and bile duct proliferation. | IRIS |
| Prochloraz | Dog<br>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<br>2-generation oral reproductive | - | NOAEL: 37.5<br>(parental & reproductive) | Some evidence of disruption of the male reproductive system (sperm concentration and count). | Ewence et al. (2013) |
| Propiconazole | Dog<br>1-year diet (short-term) | 0, 50, 250, 1250 ppm | NOAEL: 7<br>(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<br>90-day oral | - | NO(A)EL: 5.4 | Follicular epithelial hypertrophy and pigment deposits in thyroid. | EFSA (DAR) |
| Pyriproxyfen | Rat<br>78-week diet | 0, 120, 600, 3000 mg/kg food | NOAEL: 16.4/21.1 (m/f)<br>(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) |

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| S-metolachlor (metolachlor) | Rat<br>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<br>6-month | 0, 2, 5, 15, 50 mg/kg/d | NOEL: 2 | Decreased spleen weight. | TOXNET (HSDB) |
| Tebuconazole | Rat<br>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<br>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<br>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<br>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

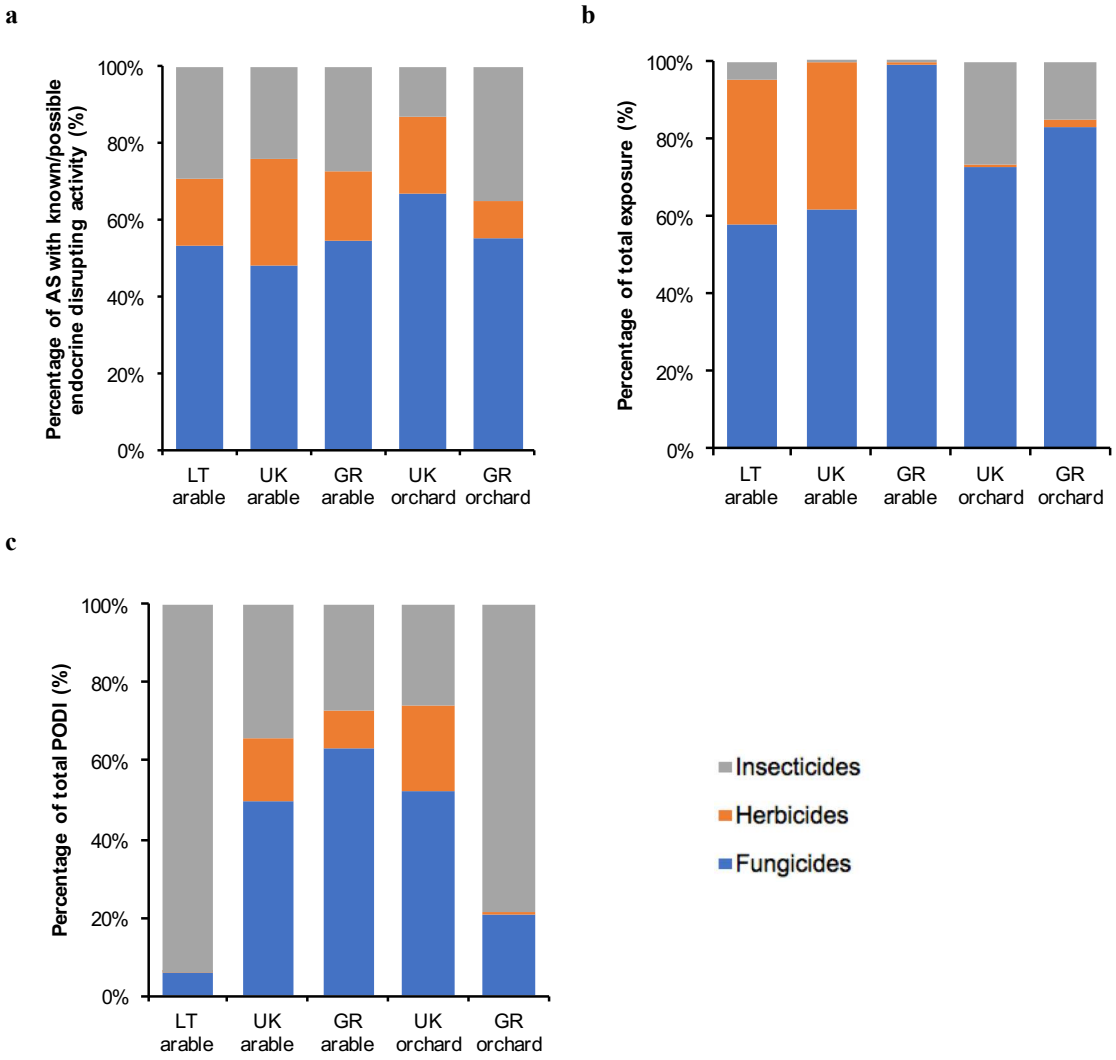


**Fig. S1** Comparison of relative contributions of fungicides, insecticides and herbicides to the total use (a), total exposure (b) and total risk (c) associated with known/possible endocrine disrupting activity across the five cropping systems over the survey period

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