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Probabilistic assessment of the cumulative dietary exposure of the population of Denmark to endocrine disrupting pesticides

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ABSTRACT

The four pesticides epoxiconazole, prochloraz, procymidone and tebuconazole, are commonly used pesticides, all suspected of acting as endocrine disrupters. In the present study, we assessed the acute cumulative dietary exposure to the women of child bearing age and the general population of Denmark to these pesticides from the intake of fruit and vegetables. The assessment was carried out using the probabilistic approach combined with the relative potency factor (RPF) approach. Residue data for prochloraz, procymidone, and tebuconazole were obtained from the Danish monitoring programme 2006–2009, while residue data for epoxiconazole were obtained from the Swedish monitoring programme carried out in the period 2007–2009. Food consumption data were obtained from the Danish nationwide dietary survey conducted in 2000–2002. Relative potency factors for the four pesticides were obtained from rat studies. Prochloraz was used as the index compound. All four pesticides increased nipple retention in male offspring, and epoxiconazole, prochloraz, and tebuconazole also increased the gestation period in pregnant rat dams. For women of childbearing age, the high-end cumulative exposure (99.9th percentile) was calculated to 9% of the Adjusted Reference Value (ARV) for the effect on nipple retention and to 1% of the ARV for the effect on increased gestation period.

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1. Introduction

Risk assessment of pesticides is currently based on no observed adverse effect levels (NOAELs) for individual compounds. However, human beings can be simultaneously exposed to several chemicals that may potentially contribute to a cumulative effect in the individual. Since 2005, the European Commission has required that a methodology to take into account cumulative and synergistic effects of pesticides is developed (Regulation EC No. 396/2005). To address this issue, the EFSA has published a "Scientific Opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health" (EFSA, 2009). In this opinion, the probabilistic approach, combined with the relative potency factor (RPF) approach as described by Wilkinson et al. (2000), was used to estimate the cumulative exposure to a group of triazoles which have a common mode of action. As also described in an EFSA opinion from 2008 (EFSA, 2008) and Boon et al. (2004), the probabilistic approach is needed when addressing the exposure from different pesticides present in several crops simultaneously. RPFs, which express the relative toxic potency of each compound compared to an index compound (IC), are used to normalise the residue levels for all compounds in the group. The RPF approach assumes that the effects following cumulative exposure can be predicted by the mathematical model of dose-addition. Cumulative dietary exposure calculations using the probabilistic approach combined with the RPF approach have also been used for other pesticides with a common mode of action, e.g. the organophosphorus and carbamate pesticides, which are both acetylcholinesterase (AChE) inhibiting compounds (Jensen et al., 2009; Boon et al., 2008; Caldas et al., 2006; Müller et al., 2009; US EPA, 2006a, 2007).

In this project, the cumulative human dietary exposure to epoxiconazole, prochloraz, procymidone and tebuconazole was assessed. For this the probabilistic approach was used combined with the RPF approach. The RPFs were obtained from rat in vivo studies using pregnant rat dams, described in detail by Hass et al. (2012). Hass et al. (2012) investigated whether a mixture of five environmentally relevant endocrine-disrupting pesticides at dose levels below NOAELs for the individual pesticides can lead to developmental toxicity effects in rats. In summary, the animals

Abbreviations: RPF, relative potency factor; ARV, adjusted reference value; NOAEL, observed adverse effect level; Ache, acetylcholinesterase; BW, body weight; LOR, level of reporting.

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were exposed to the five pesticides, either singly or in combination, during gestation and lactation. For two endocrine disrupter sensitive endpoints, nipple retention in male offspring and gestation period in pregnant dams, dose-response graphs were generated for each pesticide. These graphs were used to derive the RPFs used in the cumulative exposure calculations. Hass et al. (2012) investigated five pesticides, while in this article the exposure to only four were calculated. Epoxiconazole, prochloraz, procymidone and tebuconazole all increased nipple retention in male offspring while epoxiconazole, prochloraz and tebuconazole all increased the gestation period (Hass et al., 2012). Mancozeb was not included in the assessment because this substance did not increase nipple retention or the gestation length. Since endocrine-disrupting effects are relevant for women of childbearing age, cumulative dietary exposure calculations were performed for Danish women aged 15–50. To be able to compare the calculated dietary exposure for women of childbearing age with the general population, the calculations were also performed for the Danish general population, 4–75 years old. All these exposure calculations were performed using Danish consumption and residue data.

2. Materials and methods

2.1. Food consumption data

Intake estimates were based on consumption data obtained from the Danish National Dietary Survey 2000–2002 (Andersen et al., 2005). This cross-sectional survey included 4068 participants aged 4–75 years old drawn from the Danish Central Person Register. The participants can be characterised as close to representative for the Danish population. Women aged 15–50 accounted for 1176 participants. Dietary intake was recorded for seven consecutive days. A pre-coded food diary was used that included answering categories for the most commonly eaten foods and dishes in the Danish diet. The food diary was organised according to a typical Danish meal pattern (breakfast, lunch, dinner and snacks). Portion sizes were given in predefined household measures or estimated from photographs. Data was collected over the whole year to take into account seasonal variation in dietary habits. The response rates for completing the pre-coded food diaries were 71% for children (4–14) and 50% for adults (15–75). Self-reported body weight was obtained from a personal face-to-face interview and used in the exposure calculations. The survey has been validated and the uncertainties in the survey are described by Biltoft-Jensen et al. (2009).

2.2. Pesticide residue data

Residue data for the three pesticides, prochloraz, procymidone and tebuconazole, were obtained from the Danish pesticide monitoring programme 2006–2009. Since epoxiconazole was not analysed in fruit and vegetables in the period 2006–2009, residue data for epoxiconazole were obtained from the Swedish pesticide monitoring programme 2007–2009. However, this pesticide was only found in one sample, namely one leek out of 14 tested leeks, and not in any other tested fruits or vegetables.

The residue data included a total of 3203 samples of fruits and vegetables. The sampling plans were set up to ensure compliance with the maximum residue limits set in the legislation and taking into account the commodities that contribute most to residue intake. Only commodities with at least one detectable residue above the level of reporting (LOR) were included in the calculations. The pesticides selected were found in 21 different commodities.

To get the most realistic picture of the intake of pesticides, it is important to address processing factors. The pesticides included in the calculations were found in commodities as citrus fruits and water melon for which processing factors for peel/pulp distribution are normally applied in a refined exposure calculation. In the present study a processing factor of 0.1 was applied as described in the Danish monitoring programme (Poulsen et al., 2005).

Residue levels below the LOR can be handled in different ways. In theory, samples with levels below the LOR could contain residues somewhere between zero and LOR. For comparison both 1/2 LOR and zero was used in the cumulative exposure calculations for the effect on nipple retention. A comparison was only performed for the exposure caused by the effect on nipple retention because the exposure was about ten times higher than the exposure caused by the effect on gestation length. Only non-detect samples of commodities with at least one level > LOR were assigned 1/2 LOR. Commodities with only non-detects were assumed to contain no residue in both the 1/2 LOR and zero scenario.

2.3. Relative potency factor (RPF) approach

In the study by Hass et al. (2012), two common endocrine-sensitive endpoints were affected in the rats. One was the increased gestation period in dams treated with the pesticides, and the benchmark dose (BMD) for this endpoint was based on an increase of 0.2 days for the group mean e.g. a gestation period of 23.2 days rather than 23.0 days, (Hass et al., 2012). The other effect was increased nipple retention in male offspring, and here the BMD was based on an increase of 1 nipple for the group mean e.g. a mean of 1.1 nipples in an exposed group compared to 0.1 in the control group (Hass et al., 2012).

The benchmark doses to increase nipple retention and prolong gestation length described by Hass et al. (2012) were used to derive a so-called Adjusted Reference Value (ARV) by dividing the BMD by a safety factor of 1000. This factor was derived by including:

– The default uncertainty factor of 100 for Lowest Observable Adverse Effect Level (LOAEL).
– A factor of 3 because the effects are close to No Observable Adverse Effect Level (NOAEL).
– A factor of 3.3 to take into consideration the exposure to other endocrine-disrupting substances.

Relative potency factors for each pesticides were developed based on the low end of the dose response graphs in the rat studies because humans are expected to be exposed to low doses. Prochloraz was selected as the index compound for the exposure calculation because this compound was the best studied compound within the group with regard to effects on gestation period and nipple retention (Hass et al., 2012).

The residue concentration for a given pesticide was multiplied by the RPF value for this substance to give an equivalent content of the index compound. The residue levels per sample are summed up resulting in a cumulative residue level per sample. These data are then used to assess the cumulative exposure, which can be compared to the ARV. Bench Mark dose, relative potency factors, uncertainty factors and Adjusted Reference Values for the two effects are shown in Tables 1 and 2.

2.4. Probabilistic acute intake calculations and uncertainty analysis

The cumulative acute exposure and the acute exposure per pesticide were calculated using the Monte Carlo Risk Assessment program (MCRA 6.2), which is an internet-based program (De Boer and Van Voet, 2007). The calculations were performed as follows: A person was randomly selected from the consumption database. The consumption of each relevant commodity that person has eaten in one day was then multiplied by randomly selected normalised summed residue concentration per commodity from the residue database. The intake was then summed by commodities giving an empirical estimate of the acute cumulative intake of that individual on that specific day. This calculation was repeated 100,000 times for women of childbearing age, and the general population, giving a probability distribution for the pesticide intake.

No variability factors were used in the cumulative exposure calculations because at the time when the calculations were performed no agreed methodology on how to take variability into account in probabilistic exposure calculations existed. Variability factors accommodate for potential inhomogeneous residue distribution among the individual units in a composite sample, by taking into account the fact that an individual unit can contain higher residue levels than the composite sample.

All estimates of possible intakes were adjusted for the individual body weights for each participant. The exposures were specified at percentiles P50, P90, P95, P99, P99.9 and P99.99 and compared to the ARV for prochloraz. The 99.9th percentile was used as reference point. The uncertainty due to sampling uncertainty of the input data (concentration and consumption) was estimated using the bootstrap approach (Manly, 1998; Boon et al., 2004; Vose, 2000). This uncertainty was expressed per exposure percentile as a 95% confidence interval.

3. Results

3.1. Food consumption and residue data

Table 3 shows a summary of the food consumption data from the nationwide survey. Data are shown for both women of childbearing age and the general population. Of the foods that contained at least one positive level of the pesticides under investigation, the highest mean consumption levels were of carrots, followed by cucumber, tomato and oranges. This was seen both for the general population and for women of childbearing age. On consumption days only, the highest mean consumption was of melon, followed by table grapes, peaches and oranges for both consumer groups.

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