Health Effects of Resorcylic Acid Lactones

Subjects: Others

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Zearalenol and zearalenone are two resorcylic acid lactones known for their potent estrogenic effects. They are considered as toxic compounds from the mycotoxin category and are mainly produced by *Fusarium* fungi. Their estrogenic action made them either beneficial or toxic according to the physiological situation they are tested in. Here are reported the exposure recorded in humans as well as their blood levels. Then, beneficial and adverse effects observed *in vivo* essentially in animal models are analysed.

resorcylic acid lactones

1. Human Exposure and Bioavailability

1.1. Exposure According to Diet

As already mentioned, zearalenol and zearalenone are mycotoxins and as such they are carefully monitored in human food. A recent study led in Spain, reported the occurrence of zearalenone in food and in human urine [1]. They estimated the Probable Daily Intake and compared it to the Tolerable Daily Intake (25µg/kg/day). They found that, currently, the estimated daily intake was higher than the Tolerable Daily Intake and found that 10% of the urine samples analyzed, had quantifiable levels of zearalenone. Again, zearalenone and zearalenol being toxic, their bioavailability has only been reported in rats and not in humans.

1.2. Blood Concentrations

As previously mentioned, zearalenone and zearalenol are mycotoxins that are carefully monitored, therefore, the plasma levels are currently low and below the detection limit, in the majority of cases. According to [2] who analyzed several mycotoxins in the serum of 260 Chinese rural residents, “zearalanone” was detected in 1.2% of samples between 0.164 and 0.346 µg/L (0.05 and 0.1nM) and zearalenone was detected in 6.5% of serum samples between 0.063 and 0.418 µg/L (0.02 and 0.13 nM). Although these levels were low, other mycotoxins –including aflatoxin B1, deoxynivalenol, ochratoxin A and fumonisin– were also detected or measured, raising the question of a cocktail effect of all these substances.

2. Beneficial Effects

2.1. Hormonal Effects

2.1.1. Menopausal symptoms

Resorcylic acid lactones being considered as toxic compounds, no data were found on their potential effects on climacteric symptoms of menopausal and peri-menopausal women in interventional studies. Beside, considering the careful management of crops used for human diet and potentially contaminated by fusarium the exposure, even through food supplements, is likely to be low.

2.1.2. Bone health

Because of their toxicities zearalenone and zearalenol were not studied for their effects on human bone health. However, some data obtained *in vitro* on bone cells confirmed the estrogenic effects of zearalenone and metabolites [3]. Such effects are also documented *in vivo* in rats or rabbits [4]. Again, the prevention of bone loss is linked to an estrogenic effect [5]. However, in some studies chromosomal aberrations were also reported [6] and publications included.

2.1.3. Estrogen responsive tissues

Several data indicated that zearalenone and metabolites might be deleterious for breast cancers [7]. In addition, in the case-control study led in Tunisia on 110 women (69 cases and 41 control) [8], it was shown that the higher odd ratio was significantly associated to high level of zearalenone and metabolites in urine. Indeed, breast cancer occurrence showed a statistically significant association with urinary concentrations of a-zearalenol (OR = 1.56; 95% CI = 1.15-2.59) in the unadjusted regression model. When the model was adjusted for age, number of children, social class, type of water consumed and vegetable consumption, urinary concentration of a-zearalenol remained significantly associated with breast cancer risk (OR = 1.54; 95% CI = 1.10–2.78).

2.2. Metabolic Beneficial Effects

2.2.1. Effect on cholesterol

No data were found on the potential effect of zearalenone on cholesterol blood levels. However, an old study reported that both coumestrol and “zearanol” were able to lower cholesterol in rat [9]. In this study the effect of genistein was much lower and the tested doses were 0.1, 1 and 10 mg/kg/day.

2.2.2. Effect on metabolic syndrome

There are no data exploring the effect of zearalenone on blood and lipid metabolisms in humans. However, considering the incidence of zearalenone contamination in pig farming, several studies dealing with the effect of zearalenone supplementation on the metabolic biomarkers in pigs were published. In [10] where zearalenone was tested at 680 and 1620 µg/kg, the mycotoxin was found to be a natural metabolism-disrupting chemical. It was shown to have an impact on lipid and glucose blood concentrations. The pattern was somehow complex, with a dose and time effect. Globally, lipoproteins tended to be increased by zearalenone after 7 days but not after 21 days of treatments and cholesterol was only increased at the lowest dose after 7 days of treatment. Blood glucose was reduced at 21 days but increased with the low dose at 7 days. The effects were only mildly significant. The authors also noted that zearalenone altered circulating adipokines concentrations, inducing significant changes in

adiponectin, resistin, and fetuin B. In [11], which tested low exposure of zearalenone in gilt in sub-chronic exposure *i.e.* 40 µg/kg/day, blood glucose was not consistently modified between the experimental and control groups over 6 weeks of exposure. When the experiment was designed, 40µg/kg/day was considered as the NOAEL but it was reduced to 10 µg/kg/day while the experiment was ongoing.

2.2.3. Effects on diabetes

To researchers' knowledge, no beneficial effect of zearalenone and zearalenol were ever reported on diabetes diseases in animals and humans.

3. Adverse Effects

3.1. Reference Doses

A reference dose for reproductive physiology has been defined in humans. It is 0.4 µg/kg bw/day. It derives from a NOAEL established in pig [12] that was determined to be of 40µg/kg/day. Nowadays in France the potential human exposure has been determined at 0.042 µg/kg bw/day [13].

3.2. Hormonal Based Effects

3.2.1. Pituitary interactions

Zearalenone and zearalenol as mycotoxins occurring in cattle diet have been shown to induce major economic losses affecting animal growth and reproduction. Therefore, they have been extensively studied in animal models including pigs. In this species, they were shown in [14], to significantly reduce FSH synthesis and secretion but the resorcylic acid lactones had no effect on LH. The study also showed that both mycotoxins acted through the estrogen membrane receptor GPER. However, in the study by He *et al*., the doses used were huge *i.e.* 7.5 mg/kg/body weight intravenously administrated. Again, a dietary exposure would most probably require higher dosages to be efficient, due to the poor bioavailability of zearalenone and zearalenol after dietary intake. In parallel, the oral administration of 10 mg/kg/body weight to rats [15] was able to increase GnRH expression in the hypothalamus and to significantly decrease progesterone level in serum. The effects on FSH and LH were not significant.

3.2.2. Estrogen based toxic effects

On a cohort of 163 girls from New Jersey, it was shown that urinary zearalenone and its metabolites were associated with slower growth and pubertal development [16]. The mycotoxins were detected in 78% of the urine samples and the levels were at a median of 1.02 ng/mL, and in a range of 0–22.3 ng/mL. Conversely, in China, [17] showed that among many other factors including familial environment, zearalenone and its metabolites were strongly associated with idiopathic precocious puberty. This apparent discrepancy may be linked to the dose of exposure. According to a recent review [18], there are no epidemiological data on the reproductive effects of

zearalenone and its metabolites. However, many data are available in rodent models showing that at doses from 0.2 mg up to 146 mg/day the mycotoxins can: alter follicular profiles in the ovary of non-pregnant females, disrupt oestrus cycling and increase myometrium thickness. In addition, during pregnancy, zearalenone and metabolites are related with placental haemorrhage, stillbirth, and impaired foetal growth. In males, a recent review [19] showed that zearalenone and its metabolites increased relative epididymis weight, increased serum estradiol level, and decreased LH levels in rats exposed prenatally. In pubertal and adult rodents, the relative testicular weight, serum estradiol level, Leydig cell number, and percentage of ST (+) Leydig cells decreased under zearalenone exposure. In all animals, serum testosterone level, sperm concentration and sperm motility rates were decreased. According to the authors, zearalenone could decrease serum testosterone level at 50 µg/kg bodyweight/day, 1.4 mg/kg bodyweight/day, and 84 mg/kg bodyweight/day, in rodents exposed prenatally, at the onset of puberty and in adulthood, respectively. Sperm quantity and quality was impaired in rodent at puberty with 1.4 mg/kg bodyweight/day of zearalenone while in adults the same effect was observed at the dosage of 84 mg/kg bodyweight/day. Such effects can be considered as estrogen related toxic effects.

3.2.3. Thyroid based toxic effects

Zearalenone and metabolites being used in cattle as growth factors [20], there are several studies reporting thyroid dysfunction in animals under resorcylic acid lactone treatments [21]. A toxicological study was published in 1982 [22] testing 0, 0.1, 1 and 10 mg/kg bodyweight of zearalenone in Wistar rats. It showed a dose-related increase in absolute and relative thyroid gland weights in both males and females of the F0 and F1 generations. The effect was most important in F0 males. This effect on thyroid weight was probably a result of the estrogenic activity of zearalenone. However, at those dosages no effects were observed in the ovaries, testes, uterus, seminal vesicles and prostate gland, despite the decrease in reproductive performances.

4. Conclusions

Zearalenol and zearalenone are considered as toxic substances in human and sometimes used as growth factors in cattle. This illustrates the dual effects of phytoestrogens that can be both beneficial or adverse according to the physiological status of their consumers.

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