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Risk assessment for pyrrolizidine alkaloids detected in (herbal) teas and plant food supplements

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ABSTRACT

Pyrrolizidine alkaloids (PAs) are plant metabolites present in some botanical preparations, with especially 1,2-unsaturated PAs being of concern because they are genotoxic carcinogens. This study presents an overview of tumour data on PAs and points of departure (PODs) derived from them, corroborating that the $BMDL_{10}$ for lasiocarpine represents a conservative POD for risk assessment. A risk assessment using this $BMDL_{10}$ and mean levels of PAs reported in literature for (herbal) teas, indicates that consumption of one cup of tea a day would result in MOE values lower than 10 000 for several types of (herbal) teas, indicating a priority for risk management for these products A refined risk assessment using interim relative potency (REP) factors showed that based on the mean PA levels, 7(54%) of 13 types of (herbal) teas and 1 (14%) of 7 types of plant food supplements (PFS) resulted in MOE values lower than 10 000, indicating a priority for risk management also for these products in particular. This includes both preparations containing PA-producing and non-PA-producing plants. Our study provides insight in the current state-of-the art and limitations in the risk assessment of PA-containing food products, especially (herbal) teas and PFS, indicating that PAs in food presents a field of interest for current and future risk management.

1. Introduction

Pyrrolizidine alkaloids (PAs) are naturally occurring chemicals which are produced by a large number of plants (Griffin et al., 2013). To date, more than 660 PAs and PA *N*-oxides have been identified from an estimated 6000 plants (Bodi et al., 2014). Especially 1, 2-unsaturated PAs are hepatotoxic and considered as genotoxic carcinogens, thus posing a potential risk to human health (Mori et al., 1985). The 1, 2-unsaturated PAs can be subdivided by the type of esterification in monoesters, open chained diesters and cyclic diesters (Fig. 1). In addition, cyclic diester PAs with an azacyclooctenone, instead of a 1, 2-dehydropyrrolizidine ring system, form a special class (Fig. 1).

Botanical preparations such as (herbal) teas and plant food supplements (PFS) are widely used around the world. However, these preparations have recently been shown to frequently contain toxic PAs (Bodi et al., 2014; IPCS, 1988; Mulder et al., 2015). Bodi et al. (2014) together with the Federal Institute for Risk Assessment (BfR) in Germany who also reported part of the data (BfR, 2013), analysed seven types of herbal drugs (41 samples) and 11 types of (herbal) teas (282 samples) all supposedly to be derived from non-PA-producing plants. The results showed that (herbal) teas can contain significant levels of PAs of up to 5647 μg/kg dry material, while in herbal drugs the total PA level could reach up to 3099 μg/kg (Bodi et al., 2014). The PAs present in the (herbal) teas and PFS were suggested to originate from contamination with PA-containing weeds during harvesting. Mulder et al. (2015) analysed four types of PFS (110 samples) which were derived from non-PA-producing plants, pollen-based supplements (29 samples) and two types of PFS (39 samples) which were derived from PA-producing plants. These authors also analysed eight types of (herbal) teas (169 samples) which were derived from non-PA-producing plants and five types of (herbal) teas (12 samples) derived from PA-producing plants. For (herbal) teas and PFS which were derived from non-PA-producing plants, the level of PAs amounted up to 4805 and 8488 μg/kg in dry material, respectively.

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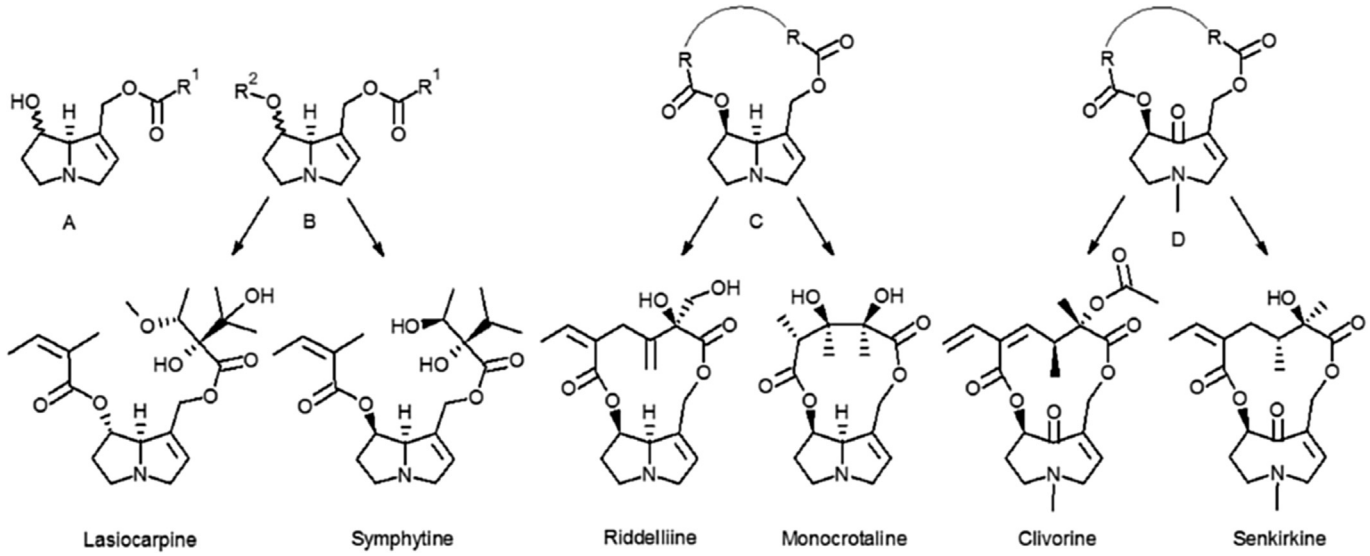

Fig. 1. Chemical structures of PAs subdivided by the type of esterification: 1,2-dehydropyrrolizidine with A: monoester; B: open chained diester; C: cyclic diester. D: azacyclooctenone cyclic diester).

For (herbal) teas and PFS which were derived from PA-producing plants, the levels of PAs amounted up to 31 101 μg/kg in specific teas (as dry material) and to 2 410 275 μg/kg in PFS (Mulder et al., 2015) (Note: In March 2017 the PA levels reported for 13 herbal tea samples in the study of Mulder et al. (2015) have been revised. Consequently, EFSA will publish a revised version of the original scientific report on the internet (Patrick P.J. Mulder, patrick.mulder@wur.nl). The revised levels have been taken into account in the calculations). These data showed that the highest values were obtained for (herbal) teas and PFS produced from PA-producing plants, but that PAs are also present in samples produced from non-PA-producing plants. Recently, upon a request form the European Commission, the European Food Safety Authority (EFSA) published a dietary exposure assessment reporting estimates for chronic and acute exposure to PAs using the PA data collected and available in the EFSA Chemical Occurrence database (EFSA, 2016a). The data on tea and herbal infusions were submitted by several data providers including five national authorities, and consisted of data provided by tea producers and traders organised in Tea & Herbal Infusions Europe (THIE), as well as data provided by Bodi et al. (2014) and Mulder et al. (2015). EFSA expressed the PA levels per liter of tea infusion as consumed dividing the level in μg/kg dry material by 75 assuming 100% extraction of the PAs present in 2 g of tea into 150 mL of boiling water. The 95th percentile values amounted up to 773 μg/kg for individual dry (herbal) tea samples and 55 459 μg/kg in PFS, including data from material from PA-producing plants (EFSA, 2016a,b).

In the studies reported by Bodi et al. (2014), Mulder et al. (2015) and EFSA (2016a), no risk assessment was presented for the PA levels detected. Given that 1,2-unsaturated PAs are considered to be genotoxic and carcinogenic, the risk assessment can best be done by applying the Margin of Exposure (MOE) approach (EFSA, 2011). To calculate the MOE for a particular compound preferably a $BMDL_{10}$ from a carcinogenicity study (benchmark dose lower confidence limit for 10% extra risk on tumour formation above background levels) is normally used as a point of departure (POD). So far, suitable experimental data to derive such $BMDL_{10}$ values have only been reported for two PAs, lasiocarpine and riddelliine (NTP, 1978; NTP, 2003). For lasiocarpine EFSA calculated a $BMDL_{10}$ of 0.07 mg/kg bw/day based on data for induction of liver haemangiosarcomas in male rats and used this as POD for comparison with the estimated dietary exposure resulting from the presence of PAs in retail honey (EFSA, 2011). EFSA indicated that the carcinogenic potency of most PAs present in honey is likely to be lower than that of lasiocarpine and that a risk characterisation using the $BMDL_{10}$ for lasiocarpine is considered a conservative approach. This is based on the consideration that lasiocarpine is amongst the most toxic of the PAs that have been tested based on the LD_{50} upon a single intraperitoneal (i.p.) dose (COT, 2008), and the fact that toxicity may be associated with the carcinogenicity. This assumption is in line with the fact that for riddelliine a $BMDL_{10}$ of 0.18 mg/kg bw/day was calculated based on the incidence of liver haemangiosarcomas in female rats (EFSA, 2011; NTP, 2003). In addition to lasiocarpine and riddelliine, other PAs, including monocrotaline, clivorine, senkirkine and symphytine, (Fig. 1), have been shown to cause tumours in animal bioassays (Hirono et al., 1979; Kuhara et al., 1980; Shumaker et al., 1976). Monocrotaline has been classified as a Group 2 B carcinogen (possibly carcinogenic to humans) by the International Agency for Research on Cancer (IARC), while senkirkine and symphytine have been classified as Group 3 (not classifiable as to its carcinogenicity to humans (IARC, 1976; IARC, 1983; IARC, 2002). For these PAs available tumour data are not suitable for dose response modelling and definition of $BMDL_{10}$ values, but their data could still be used to provide a better estimate of how conservative the use of the $BMDL_{10}$ of lasiocarpine for risk assessment on 1,2-unsaturated PAs would be. PODs for calculating the MOE in situations where the data do not facilitate dose-response modelling to obtain a $BMDL_{10}$ are the T25 and/or T10 values, representing the dose levels resulting in 25 or 10% tumour incidence above back ground levels after lifetime exposure (BfR, 2009; EFSA, 2005). In their opinion on a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic EFSA already indicated that in cases where the data would be unsuitable for deriving a $BMDL_{10}$, use of the T25 is recommended (EFSA, 2005). EFSA also indicated that when using the T25 for calculation of the MOE a value of 25 000 instead of 10 000 could be used to judge if the MOE indicates a priority for risk management (EFSA, 2005). To facilitate comparison to other genotoxic carcinogens BfR derived an MOE based risk assessment for glycidol and its esters, using the T10 calculated from the T25 by