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Accumulation and decontamination kinetics of PCBs and PCDD/Fs from grass silage and soil in a transgenerational cow-calf setting

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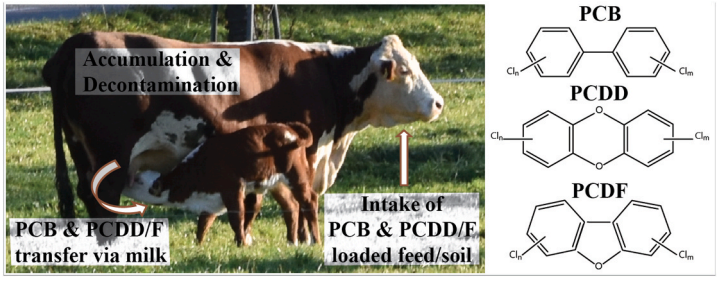
HIGHLIGHTS

- Transgenerational transfer of PCBs & PCDD/Fs in cattle exposed to contaminated soil.
- Lower transfer rates of POPs to cow milk were associated with lower milk fat yields.
- Longer two-phased milk elimination half-lives were linked to lower milk fat yields.
- Increases in calves' body fat mass efficiently diluted PCBs & PCDD/Fs.
- Decontamination via growth dilution seemed more efficient than via milk excretion.

GRAPHICAL ABSTRACT



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ABSTRACT

Polychlorinated biphenyls (PCBs) and dibenzo-*p*-dioxins/dibenzofurans (PCDD/Fs) are bioaccumulative pollutants that endanger bovine food safety. Bioaccumulation depends, among others, on the physiological dynamics of the cow's reproductive cycle. However, recent studies have focused only on near steady-state situations. Thus, the effects of animal physiology on PCB + PCDD/F transfer from grass silage and soil to cows' blood, adipose tissue, and milk and subsequently to suckling calves during gestation and lactation were investigated. In the exposed group, nine cows ate a grass silage/contaminated soil mixture (6.6 ± 0.8 μg iPCBs and 2.6 ± 0.4 ng dlPCB + PCDD/F TEQ kg_{DM}^{-1}) for 109 days prepartum until 288 days in milk (DIM). Four of these cows underwent decontamination after DIM164, receiving the same clean grass silage as the four control cows during the experiment. Calves were fed the milk of their respective mothers. In the exposed group, transgenerational bioaccumulation occurred until DIM164, with calf blood and adipose tissue PCB + PCDD/F concentrations reaching levels twice as high as those in their respective mothers. Transfer rates from oral intake to milk ranged from 0.1 up to 42%, depending on pollutant congener, dietary treatment, and reproductive parity of the cow. Congener

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and parity also influenced the decontamination half-lives of milk. In decontaminated calves, declines in adipose tissue PCB + PCDD/F concentrations coincided with increases in body fat mass. Therefore, it is essential to know the physiological characteristics of cattle, exposure dose and duration, and physicochemical compound properties to perform reliable transfer assessments.

1. Introduction

Polychlorinated biphenyls (PCBs) and dibenzo-*p*-dioxins/dibenzofurans (PCDD/Fs) are persistent organic pollutants (POPs), listed by the United Nations Stockholm Convention (EFSA, 2018; Stockholm_Convention, 2022). Both compounds are easily dispersed, resistant to environmental degradation, and bioaccumulative (Bogdal et al., 2017), which raises concerns for humans. They exhibit several adverse health effects, as they are endocrine disruptors, carcinogens, and neurotoxins (EFSA, 2018; Guo et al., 2019). In Western countries, food of animal origin (meat, dairy, eggs and fish) accounts for >90% of human exposure to PCBs and PCDD/Fs (EFSA, 2018; U.S.EPA, 1994). Moreover, 1–53% of Europeans exceed the tolerable weekly intake (TWI), which is an underestimation, since the European Food Safety Authority recommended reducing the TWI by a factor of seven (EFSA, 2018).

Bovine meat (beef and veal) accounts for 18% of humans' exposure to PCBs and PCDD/Fs (BAG, 2013; Ryan et al., 2013; Saktrakulkla et al., 2020). Among various beef production systems, grass-based extensive suckling beef husbandry is more prone to exceeding regulatory levels (BAG, 2012; Weber et al., 2015; Zennegg, 2018). This may result from higher exposure to PCBs and PCDD/Fs, especially from soil intake due to extensive grazing (Jurjanz et al., 2012) and from specific physiological features that increase POP accumulation in milk and meat, such as low milk yield and mother-calf bioaccumulation. Such livestock POP contamination incidents primarily threaten livestock system sustainability. Contaminated herds are typically slaughtered and incinerated, which compromises consumer confidence, harms the agri-food chain economy, and induces social distress among farmers (Rychen et al., 2014).

To ensure the chemical safety of bovine food products, it is necessary to understand the fate of PCBs and PCDD/Fs coming from diffusive sources, especially in the context of grass-based suckling beef husbandry, where soil intake can be problematic. To date, the relevant research, most of which has centered on high-yielding dairy cows, has consisted of short- to medium-term studies (1–167 d of exposure) that took place halfway through the lactation period (Amutova et al., 2020; Lorenzi et al., 2020; Piskorska-Pliszczynska et al., 2017). Additionally, these studies focus only on a few congeners and compartments (e.g., milk) and include poor descriptions of animal physiology. Data on pre-weaning calves are even more scarce, with only one or two sampling time points, omitting individual intake and other key physiological traits (Hirako, 2008a, b; Hirako and Endo, 2016; Keller et al., 2001; Rychen et al., 2011).

Such limitations have forestalled exploration of the effects of physiological changes that occur during gestation and the entire lactation period on PCB and PCDD/F accumulation and decontamination kinetics in key body distribution (blood), storage (adipose tissue), and excretion (milk, feces) compartments. Indeed, during the reproductive cycle, major changes occur in the dynamics of suckling cow and calf feed intake, body lipid mass, milk yield, and fecal excretion. Such dynamic patterns in dietary and body lipids have been shown to affect the transfer and decontamination rates of PCBs in growing bulls (Driesen et al., 2021) and adult ewes (Rey-Cadilhac et al., 2020) but deserve further attention in low-yielding lactating cows and pre-weaning calves.

The aims of this study were (i) to quantify the accumulation and decontamination of PCBs and PCDD/Fs from grass silage and soil to blood, adipose tissue and milk of cows and calves; and (ii) to link PCB and PCDD/F fate to physiological changes that cows and calves experience during gestation and lactation, resulting, to the best of our knowledge, in the largest and longest transgenerational setup. The physiological focus herein relied on body and milk lipid dynamics, since it was hypothesized that the lactation stage and parity would have an effect on lipophilic POP fate.

2. Materials and methods

2.1. Animals and diets

The cattle experiment was approved (n°2018_08_FR) by the committee on animal experimentation of canton Fribourg (CH) and took place at the experimental farm Agroscope (Posieux, CH). Seven pregnant and dry Simmental heifers [754 ± 45 d old, 502 ± 62 kg body weight (BW)] and six pregnant and dry Simmental cows (1269 ± 290 d old, 587 ± 21 kg BW, 2.3 ± 0.8 parities) were purchased from Swiss dairy farms. After four weeks of adaption, the experiment started 109 ± 11.5 d prepartum, and lasted until 288 ± 4.5 days in milk (DIM).

Of the 13 heifers and cows (hereafter referred to as cows), four were assigned to the control group and nine to the exposed group based on parity, BW, body condition score (BCS), dry matter intake (DMI), and expected milk yield. The exposed group was further subdivided so that four cow-calf pairs could undergo a decontamination phase after DIM164 ± 4.4 (Fig. 1).

Cows were fed *ad libitum* (10% refusals) daily at 14:00 h with grass silage only (control and decontaminated treatments) or grass silage mixed with 2.5% (DM basis) environmentally-loaded soil excavated from a polluted site in Switzerland (exposed treatment; SI Section 1). Soil inclusion level was chosen based on classical ingestion values found on pasture (Jurjanz et al., 2012) and to be around the current EU's legal maximum regulatory level for dlPCB + PCDD/F TEQ in feed (1.4 ng dlPCB + PCDD/F TEQ kg_{DM}^{-1}; EU Regulation 277/2012).

At the latest 10 h after calving, the calves were separated from their mothers. Cows were milked twice daily at 06:00 h and 16:00 h, which was fully offered within 30 min to the corresponding calf via teat-equipped buckets. Calves also received *ad libitum* water, non-contaminated hay, a salt stone, and after three months of age, 208 g DM d^{-1} of concentrate at 15:00 h.

Cows were housed in a tie-stall barn with access to an outdoor walking area three times a week, whereas calves stayed in individual indoor calf boxes. At three months of age, they were moved to the tie-stall barn. Wood shavings, which were used as bedding material, were dispersed posterior to cow and calf to prevent oral intake while fixed in the tie-stall. This prevented ingestion and thus, uncontrolled route of POP exposure. Straw was exclusively used as bedding material for cows during calving (<5 d) in the calving box and for calves in the individual indoor box during their first three weeks of life.

To overcome cross-contamination, treatment groups were separated in the barn by at least one free tie-stall place of 1.5 m. For forage distribution, treatment-specific materials were used. For milking, an individual bucket milking system was applied to keep separate milk collection lines for control and exposed.

One week after calving, one calf died due to a *Cryptosporidium* infection, followed by the exclusion of its mother from the experiment. Data from these two animals were not included in any statistical analyses but appear later as single illustrative points (at least for the calf). After the change in bucket position and teat removal for milk distribution, two additional calves died suddenly at three months of age. The cause of death was related to rumen milk drinking, followed by acute meteorization.

2.2. Measurements, sampling, and analyses

Daily individual DMI was based on individual fresh matter intake and DM content of the offered and refused grass silage or grass silage-soil mixture. The offered fresh diets and refusals were individually weighed 4 d week^{-1} during distribution into individual troughs. Subsamples of fresh diets and individual refusals were collected 2 d week^{-1} (further pooled weekly for refusals) to determine the DM content (103 °C, 24 h) of each.

Additionally, pools per lot of grass silage, grass silage-soil mixture, hay, minerals, salts, and concentrate were composited for chemical and POP analyses from subsamples collected weekly during the experiment (see SI Section 2, Table S8 for details of the chemical analyses).

Cow and calf BWs were recorded just before forage distribution weekly until DIM60 and every two weeks thereafter, whereas cow BCS (scale 1–5) (Edmonson et al., 1989) was recorded every two weeks until DIM30 and every four weeks thereafter. Subcutaneous adipose tissue thickness was recorded via ultrasound imaging between the ischium and sacrum (SI Section 3) at DIM1, 29, 89, 164, and 288, as well as on DIM199, 227, and 255 for the decontaminating animals.

Once a week, individual milk samples composed of two consecutive evening and morning milking sessions, based on respective milk yields, were preserved with bronopol-B2 and analyzed for fat, protein and lactose content, and somatic cell count (Institut Agricole de Grangeneuve, Posieux, CH) using mid-infrared spectrometry (Milkoscan FT+ and Fossomatic FC200, Foss Electric, Hillerød, DK) (Cunniff and AOAC, 1997). Milk samples were collected on DIM1, 7, 14, 21, 29 ± 1.4, 59 ± 1.4, 89 ± 1.8, 127 ± 2.7, 164 ± 4.4, 229 ± 4.5, and 288 ± 4.5 as well as on DIM167 ± 4.8, 171 ± 4.7, 178 ± 4.7, 185 ± 4.7, 199 ± 4.7 and 255 ± 4.7 (mean ± standard deviation) for the decontaminating cows (i.e., decontamination days +3, +7, +14, +21, +35, +63, +91 and +124). One subsample was analyzed using mid-infrared spectroscopy, as detailed previously, and a second one (300 mL) was stored at −20 °C, pending POP analyses.

Cow and calf blood samples were collected for beta-hydroxybutyrate and lipid classes (9 mL) and POP (180 mL) analyses before morning milking and feeding via jugular vein venipuncture (SiO_2-coating; Greiner Bio-One™ VACUETTE™, Kremsmünster, AT) at DIM-109 (for cows only), 1, 29, 60 (for calves only), 89, 164, and 288, as well as on 199, 227, and 255 for the decontaminating animals. For POP analyses, 500 mL of blood was collected at slaughter (DIM288) during exsanguination. After 1 h, the blood serum was separated via centrifugation (3000 *g*, 15 min, ambient temperature). For POP analyses, 100–150 mL (from slaughter, 200–300 mL) of blood serum was harvested and stored at −20 °C. Beta-hydroxybutyrate and lipid class analyses were performed using commercially available kits (SI Section 4).

Cow and calf pericaudal subcutaneous adipose tissue (5–10 cm above the tail head; SI Section 5) was harvested via biopsy at 08:00 h on DIM-109 (for cows), 1 (for cows), 29 (for cows), 89 and 164 for adipose cell size measurement (SI Section 6) and POP analyses. On DIM288, adipose tissue was collected at slaughter at the same anatomical site.

For PCB and PCDD/F analyses, a slightly modified previously reported analytical method was followed (Bogdal et al., 2017; Driesen et al., 2021) (see SI Section 7 for a detailed account of the procedure and quality assurance). Briefly, dry feed and soil, and fresh adipose tissue slaughter samples were Soxhlet; blood serum and milk were liquid-liquid extracted. The biopsy samples were extracted in a mortar with a 1:1 ratio of ether to *n*-pentane. Before, all extracts were spiked with $^{13}C_{12}$-labeled indicator PCB (iPCB), dioxin-like PCB (dlPCB), and PCDD/F internal standards, the lipid content was determined gravimetrically within the animal samples. Purification was based on silica, alumina, and carbon column chromatography clean-up. For the quantitative analyses of PCBs, a Q-Exactive Orbitrap GC-HRMS (ThermoFisher Scientific, MA, USA) was used, whereas PCDD/Fs were analyzed using an APGC-Xevo TQ-XS Triple Quadrupole MS (Waters, SM, USA). Excellent analytical performance was evidenced in the last EU-RL proficiency test for PCBs in feed (2020–04, Wageningen Food Safety Research). The toxic equivalent (TEQ) levels presented are based on the lower bound (nd = 0) WHO-toxic equivalency factors (TEFs) from 2005 (Van den Berg et al., 2006).

2.3. Calculations and statistical analyses

The PCB and PCDD/F concentration kinetics in milk, blood serum, and adipose tissue were analyzed by ANOVA using the MIXED procedure of SAS (version 9.4, SAS Institute Inc., NC, USA). For the full experimental period, a model for repeated measures was used, including the fixed effects of treatment (control, exposed), parity (primiparous, multiparous) nested within treatment, time (week or DIM) and their interactions, and animal as a random effect. A first-order autoregressive variance-covariance matrix was used for weekly measurements, whereas a spatial power matrix was used for DIM measurements to account for unequal time spaces between repeated measurements. A similar model was used for only the decontamination period, with either the decontaminated animals alone (without treatment effect) or with all treatments. For POP measurements, values out of order were excluded from the model but were still reported graphically as separate points. Logarithmic transformation was applied when needed to comply with

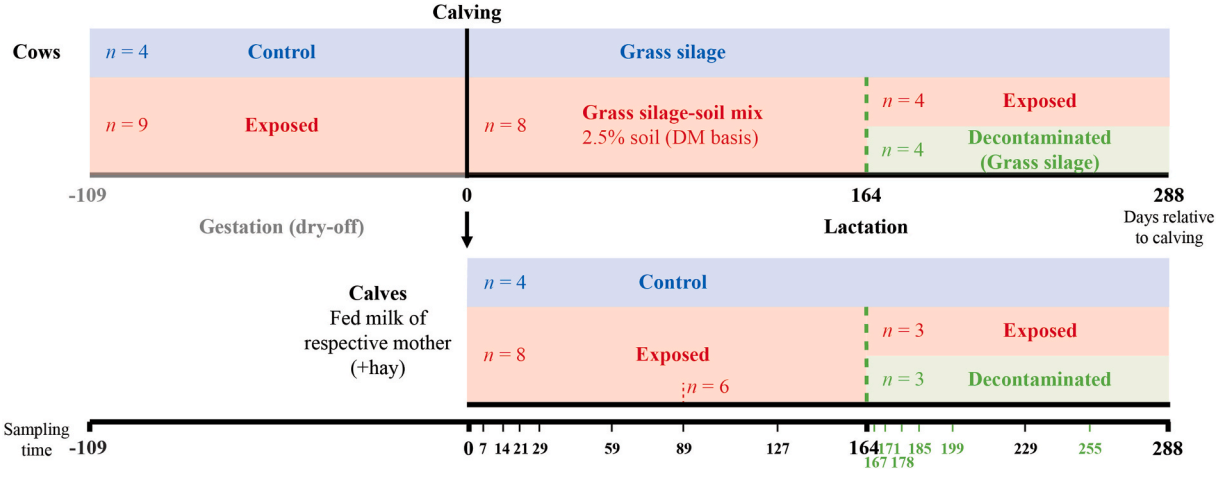

Fig. 1. Overview of the experimental design. Each treatment group equally consisted of primi- and multiparous cows, except for the gestation period, during which one additional primiparous exposed cow was present, and after DIM89 for the calves with one exposed and one decontaminated primi-calf only, due to early deaths at three months of age.

the assumptions of normality, homoscedasticity, and linearity of residuals. When transformation was needed, least squares means and standard errors were reported from untransformed data, whereas *P*-values reflected transformed statistical analyses. Significance was declared at $P \leq 0.05$ and trends at $0.05 < P \leq 0.10$.

The transfer rate to milk (TR) was calculated via (Amutova et al., 2020; Lorenzi et al., 2020):

$$TR\ (\%) = \left[(C_m \times MFY) / (C_f \times DMI)\right] \times 100 \quad (1)$$

where C_m is the congener concentration in milk (pg $g_{milk\ fat}^{-1}$), *MFY* is the daily milk fat yield ($g_{fat}\ d^{-1}$), C_f is the congener concentration in feed (ng kg_{DM}^{-1}), and *DMI* is the daily dry matter intake (kg d^{-1}).

To estimate the POP half-life ($t_{1/2} = \ln(2)/decay\ constant$) in milk during the decontamination period, the least squares means for decontaminated animals according to parity were analyzed with a two-phased non-linear model using the NLIN procedure of SAS (Tuinstra et al., 1992):

$$C = C_A \times e^{(-\alpha t)} + C_B \times e^{(-\beta t)} \quad (2)$$

where *C* is the congener concentration at a given time (pg g_{lipids}^{-1}), C_A is the initial congener concentration of the first component (pg g_{lipids}^{-1}), C_B is the initial congener concentration in the second component (pg

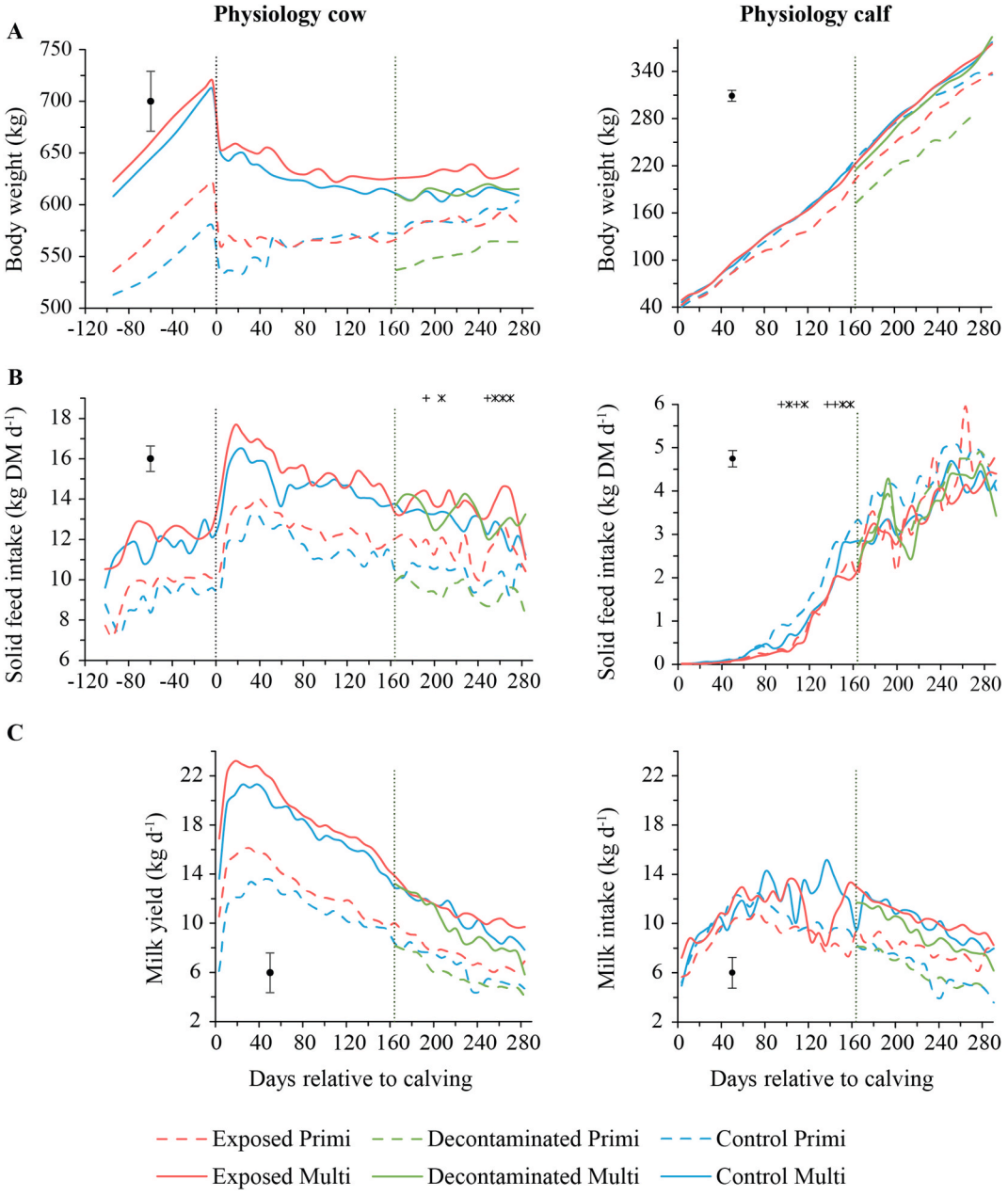

Fig. 2. Dynamics of body weight (A), solid feed intake (B), and milk yield or intake (C) of cows (left panels) and calves (right panels). The vertically dotted line at day 0 represents calving, and the one at day 164 indicates the initiation of decontamination. Least squares means and standard errors of the means are displayed. Exposed primiparous animals: for cows $n = 4$ until DIM164 and $n = 2$ thereafter; for calves $n = 4$ until DIM89, $n = 2$ from DIM89 until 164, and $n = 1$ thereafter. Exposed multiparous animals: for cows and calves $n = 4$ until DIM164 and $n = 2$ thereafter. Decontaminated primiparous animals: for cows $n = 2$, for calves $n = 1$. Decontaminated multiparous and control primi- and multiparous animals: for cows and calves $n = 2$. Trends and significant differences between the dietary treatment at the corresponding time point are indicated as follows: $^{+}P < 0.10$, $^{*}P < 0.05$. The time effect was always significant ($P < 0.05$); the parity effect always showed a trend or was significant ($P < 0.10$).

g_{lipids}^{-1}), α and β are decay constants (d^{-1}), and t is the decontamination time (d).

3. Results and discussion

This 397 d animal experiment is, to the best of our knowledge, to date the largest and longest investigation of the transgenerational fate of PCBs and PCDD/Fs from forage to cow and via milk to calf during cow gestation, the entire lactation, and calf pre-weaning growth period. The combined fine description of PCB and PCDD/F toxicokinetics together with lipid dynamics in distribution (blood), storage (adipose tissue), and excretion (milk) compartments is a key step in understanding the complex interplay between lipophilic contaminant fate and cattle physiology. Such an approach is essential for better understanding the fate of PCBs and PCDD/Fs that generally follow lipid fluxes (Driesen et al., 2021; Rey-Cadilhac et al., 2020).

3.1. Cow and calf physiological traits

Most of the cows' and calves' physiological traits showed no differences ($P > 0.10$) between dietary treatments (Fig. 2, S4, S5), suggesting no detrimental effects of PCB and PCDD/F exposure on animal performance, in accordance with previous short-term studies on dairy cows at moderate POP exposure levels (Huwe and Smith, 2005; Lorenzi et al., 2020). Calf solid feed intake constituted one exception, with a 1.1-fold higher intake for the control calves ($P = 0.04$).

Over the full experimental period, primiparous cows ate on average 1.3-fold less; their BW was 1.1-fold, milk yield 1.5-fold, and fat yield 1.8-fold lower compared to multiparous cows (13.6 ± 1.6 kg_{DM} d^{-1}, 633 ± 27.2 kg BW, 14.1 ± 4.6 kg_{milk} d^{-1}, 0.6 ± 0.2 $kg_{milkfat}$ d^{-1}, $P < 0.1$; Fig. 2, S5; Table S3). Primi-calves ate 1.1-fold more solid feed and 1.4-fold less milk, and their BW was 1.1-fold lower compared to multi-calves (2.2 ± 1.6 kg_{DM} d^{-1}, 10.5 ± 1.9 kg_{milk} d^{-1}, 197 ± 103.4 kg BW, $P < 0.1$; Fig. 2, Table S5).

After calving, cow DMI increased sharply 1.3-fold compared to prepartum, reaching a peak around DIM25 before decreasing linearly 1.3-fold by the end of lactation (Fig. 2B). A similar time trend was recorded for milk yield (Fig. 2C), as well as for blood lipid content, which is driven by nutrient flow in the duodenum (Bauchart, 1993). Conversely, milk fat content, BW, BCS, and adipose tissue cell size and thickness decreased and later increased during lactation (Fig. 2A, S4-6). Calves weighed 45 ± 5.5 kg at birth with a linear weekly gain of approximately 7.4 kg (Fig. 2A). Calf milk intake reached a peak of 9.4 ± 3.0 kg_{milk} d^{-1} around DIM80 (Fig. 2C). In addition, solid feed intake increased linearly from almost 0 kg d^{-1} at DIM40 to 4.4 kg d^{-1} at DIM288 (Fig. 2B).

With these 'classical' physiological time trends, the study fulfilled its aim of mimicking a suckling cow husbandry scenario, although the average milk yield (2997 and 4243 kg_{milk} $lactation^{-1}$ for primi- and multiparous cows, respectively) was higher compared to typical suckling cow breeds, which produce 1600–2250 kg_{milk} $lactation^{-1}$ (Sepchat et al., 2017). Nevertheless, calf milk intake (2221 and 2992 kg_{milk} $lactation^{-1}$ for primi- and multi-calves, respectively) and milk yield of some low-productive primiparous cows were still in this typical range, as well as the DMI and BW kinetics.

3.2. PCB and PCDD/F transgenerational accumulation kinetics

3.2.1. PCB and PCDD/F concentrations in feed and soil

Soil is considered an important diffusive POP source in extensive grass-based feeding systems (Schulz et al., 2005; Weber et al., 2019) and was therefore used as exposure matrix. The contamination levels of feedstuffs and soil remained constant for dlPCBs and PCDD/Fs during the experiment (Tables S7, S9). The iPCB pattern varied slightly over time, especially in terms of PCB28 and 52 concentrations, although the iPCB sum remained stable. However, the cows were mainly exposed via dlPCBs and PCDD/Fs. The grass silage-soil mixture reached concentrations of 6.6 ± 0.8 μg iPCBs and 2.6 ± 0.4 ng dlPCB + PCDD/F TEQ kg_{DM}^{-1}. Over 397 d of experiment, this led to an average oral dosing of 73 and 90 μg iPCBs, and 29 and 36 ng dlPCB + PCDD/F TEQ d^{-1} for exposed primi- and multiparous cows, respectively (4- and 26-fold higher than the control cows). The most abundant congeners in grass silage were PCB101 (33%) and PCB52 (26%) for iPCBs, PCB118 (65%) and PCB105 (21%) for dlPCBs, whereas OCDD (69%) and 1234678HpCDD (11%) dominated the PCDD/Fs (in raw concentrations). In the grass silage-soil mixture, contribution moved toward the pattern of the soil (Table S9; Figure S8), with the highest abundances being PCB153 (28%) and PCB138 (22%) for iPCBs, PCB118 (55%) and PCB105 (16%) for dlPCBs, and OCDF (69%) and 1234678HpCDF (11%) for PCDD/Fs. Further details regarding feed and soil are mentioned in SI Section 1 and Tables S1, S8, and S10.

3.2.2. Cow PCB and PCDD/F kinetics in blood serum, milk, and adipose tissue

Pre-trial background levels of iPCBs and dlPCBs + PCDD/Fs in cow blood serum and adipose tissue are reported in Tables S11-12. Accumulation dynamics were investigated in milk, blood serum, and adipose tissue (Fig. 3A–B, S9A). The detailed pattern over time for single congeners is reported in Tables S13, S15, and S17.

3.2.2.1. Initial background body levels. At the start of the experiment, the background levels in blood serum were 9.7 ± 2.7 and 7.9 ± 3.9 ng iPCBs, and 0.3 ± 0.6 and 0.4 ± 0.8 pg dlPCB TEQ g_{lipids}^{-1} for primi- and multiparous cows, respectively. In adipose tissue, 6.4 ± 3.3 and 8.7 ± 4.2 ng iPCBs, and 0.06 ± 0.02 and 0.08 ± 0.03 pg dlPCB TEQ g_{lipids}^{-1} were found, respectively. The PCDD/Fs were mostly below the limit of quantification (LOQ) (Tables S11-12).

3.2.2.2. Effects of congener physicochemical properties and dietary treatments. Exposed cows blood serum had average iPCB and dlPCB + PCDD/F concentrations 4.2- (29 ng g_{lipids}^{-1}) and 15-fold higher (7.0 pg TEQ g_{lipids}^{-1}), respectively, compared to the control cows. In milk, concentrations were 6.5- (22 ng g_{lipids}^{-1}) and 11-fold higher (8.5 pg TEQ g_{lipids}^{-1}), and in adipose tissue, concentrations were 5.5- (20 ng g_{lipids}^{-1}) and 16-fold higher (6.2 pg TEQ g_{lipids}^{-1}), respectively. At the individual congener level, absorption rates and metabolic susceptibility may vary (Mclachlan, 1993), resulting in different patterns in cow tissues compared to grass silage and soil. Overall, the most abundant congeners in cows were PCB138 and 153 for iPCBs, PCB105, 118, 156, and 167 for dlPCBs, and 123478HxCDF and 1234678HpCDF for PCDD/Fs (in raw concentrations). All these congeners are characterized by having more than five chlorine atoms, and the PCBs have a 4,4′- or 2,3,5-substitution pattern, which is the key to PCB persistence (Mclachlan, 1993; Tanabe et al., 1981). Conversely, some congeners that are abundant in grass silage, such as the low-chlorinated PCB52 and 101, were found in rather low concentrations in cows due to their high metabolic clearing potential (Figure S10) (Mclachlan, 1993).

3.2.2.3. Effects of cow physiology (parity and lactation stage). Regardless of the dietary treatment, primiparous cows showed almost constantly higher iPCB and dlPCB + PCDD/F concentrations in blood serum and milk than multiparous cows. This effect was significant ($P < 0.05$) in milk at the beginning of lactation for persistent congeners (PCB138, 153, 180, 126, 156, 157, 169, 189, 1234789HpCDF, 123789HxCDD). This might result from the lower BW and milk yield seen in primiparous cows, and the associated lower dilution and excretion capacities, respectively, compared to multiparous cows. In adipose tissue, iPCB and dlPCB + PCDD/F concentrations were also higher in primiparous cows until DIM164, but at DIM288, concentrations were higher in multiparous cows.

The highest iPCB and dlPCB + PCDD/F concentrations in blood

serum and milk were found at parturition, followed by a rapid decrease prior to DIM7 for milk. Indeed, the initiation of lactation is linked to a rapid increase in milk fat output, thereby sharply enhancing POP excretion. After DIM7, a slight upward kinetic ($P < 0.05$) occurred until the end of lactation. This might be explained by a stronger decrease in milk fat yield (2.3-fold, POP excretion) compared to forage intake (1.3-fold, POP exposure) from the beginning until the end of lactation. Conversely, PCB and PCDD/F concentrations in cow adipose tissue did not change ($P > 0.10$) during the first half of lactation, whereas a 1.2-fold decline occurred in exposed cows from DIM164 to DIM288. This may have resulted from the replenishment of cow body lipid reserves at the end of lactation, thereby expanding their dilution space for POPs (Brambilla et al., 2008), as ascertained by the positive energy balance (Figure S7) and the 1.1-fold increase in adipose cell size (Figure S5B). Therefore, over medium-term periods, adipose tissue POP concentration kinetics seem mainly driven by its lipid mass dynamics, rather than by the slow and delayed POP equilibrium that occurs between such a deep compartment and the well-perfused ones (e.g., blood and milk), as previously shown in non-lactating ewes (Rey-Cadilhac et al., 2020).

3.2.3. PCB and PCDD/F transfer rate from oral intake to cow's milk

A precise quantification of POP transfer from feed to animal-derived products is essential for risk assessment and to guarantee food safety (Amutova et al., 2020). The feed-milk TR preferentially has to be recorded during a steady-state condition (Hoogenboom et al., 2015). The detailed time trend of TRs during lactation are reported in Figures S11-12 and Table S19, whereas in Fig. 4, TRs are reported for DIM164, where a reduced variation was recognized and decontamination had not started yet, so that the largest number of cows resulted in a higher reliability.

3.2.3.1. Effects of congener physicochemical properties and dietary treatments. All studied POP congeners were transferred to milk but at different rates. Overall, the transfer of PCBs was higher compared to PCDD/Fs (Fig. 4). At the individual congener level, TRs depended on molecular weight, chlorination degree, and thereby lipophilicity (log K_{ow}) (Amutova et al., 2020), with a differential effect of such physicochemical features between PCBs and PCDD/Fs. Across PCBs, TRs increased when these three parameters increased (Fig. 4A). Therefore, the tri- to penta-chlorinated iPCBs 28, 52, and 101 showed the lowest TR (0.4–2.6%) and may be classified as labile. The hexa- and hepta-iPCB and dlPCB congeners presented higher TRs, except for PCB77 and 123 (1.0% and 2.2%). These higher TRs could further be divided into medium TRs seen for PCB81, 105, 114, and 118 (4.6–12.7%) and even higher TRs seen for the remaining ones (13.2–42%). For the non-*ortho* dlPCBs 126 and 169, a higher TR to milk was observed compared to their equally chlorinated mono-*ortho* counterparts. This effect was previously seen for other transfer factors, such as bioconcentration or biotransfer factors in growing bulls (Driesen et al., 2021). Conversely, in PCDD/Fs, TRs showed an inverse relationship to the chlorination degree (Fig. 4B) (Hoogenboom et al., 2015). The ones with the highest TRs were 2378TCDD, 12378PeCDD, and 23478PeCDF, followed by hexa-PCDD/Fs (except 123789HxCDF), whereas the highest chlorinated hepta- and octa-PCDD/Fs showed low TRs (<3%). This results from a high log K_{ow} (>8) for hepta- and octa-PCDD/Fs, which decreases the absorption rate (Mclachlan, 1993; Sweetman et al., 1999). In PCBs, the most lipophilic hepta-PCB189 reaches only a log K_{ow} of 7.6 (Amutova et al., 2020). In addition, 2378TCDF and 12378PeCDF are characterized by low TRs (<3%), as they are known to be well metabolized (Amutova et al., 2020).

The TRs between dietary treatments were similar, except for the lower TRs of PCB126 (non-*ortho*), 180, and 189 (hepta-chlorinated) in exposed compared to control cows. For the PCDD/Fs detected in control cows (123478HxCDF, 1234678HpCDF, 1234678HpCDD, and OCDD), a similar trend was observed at much lower TR levels. These differences may be related to variable exposure matrices (grass silage *vs.* grass silage-soil mixture). Soil may have reduced the bio-accessibility and absorption rate of these congeners compared to grass silage. Unfortunately, this assumption could not be tested on the other non-*ortho* dlPCBs, as these were either lower than the LOQ in control milk or diet (PCB81 and 169) or did not accumulate enough (PCB77). This putative lowering effect of soil on the bioavailability of only three congeners still remains slight, in accordance with the low soil organic carbon level (3.1%, Table S10), at which no reduction in iPCB bioavailability was observed in piglets (Delannoy et al., 2015).

3.2.3.2. Effects of cow physiology (parity and lactation stage). During the entire lactation period, a significant variation in TR over time was highlighted. The largest variation was observed at the beginning of lactation, when the largest change in milk fat yield and DMI occurred (Figures S11-12; Table S19). Parity also widely affected the TRs, with a remarkably lower TR in primi- than in multiparous cows, regardless of the congeners and treatments. Such results might seem puzzling, as it appears contradictory that milk PCB and PCDD/F concentrations are higher in primi- compared to multiparous cows. In addition, the overall TR levels recorded in the present study were largely lower than the mean levels summarized by Amutova et al. (2020), who highlighted also a wide variation in TRs among the several studies they reviewed. Such discrepancies may result, at least in part, from differences in milk production levels across parities and studies. Indeed, a concomitant 1.9-fold lower milk fat yield (TR numerator), which was not fully compensated by the 1.1-fold higher milk POP concentration (numerator) and 1.2-fold lower exposure level (denominator; i.e., DMI as diet POP concentrations are equal between parities), were seen in primi- compared to multiparous cows, leading to a net 1.3-fold lower TR. This is in agreement with literature-based comparisons (Amutova et al., 2020), in which the average milk fat yield of the high-yielding dairy cows was 2.3-fold and the DMI was only 1.5-fold higher than in cows in the present study. The dependency of TRs on milk fat yield was previously reported by Sweetman et al. (1999) and Fries et al. (1999). In addition, the parity effect observed in the present study may also be responsible for differential body fat dynamics, PCB and PCDD/F absorption, or metabolic clearance rates seen among parities.

Together, these results challenge the broad assumption that a ratio of POP input mass to excretion mass (TR) or body burden (assimilation efficiency) is mostly insensitive to animal physiological features, conversely to concentration ratios such as the bioconcentration factor (Amutova et al., 2020; Driesen et al., 2021). The fate of the remaining POPs not transferred to milk in low-yielding cows deserves further research based on a complete POP mass balance to decipher the unabsorbed, metabolized, or body-stored fractions.

3.2.4. Calf PCB and PCDD/F kinetics in blood serum and adipose tissue

Exposure of ruminants to PCBs and PCDD/Fs starts during the fetal stage via transfer across the placental barrier (Hirako et al., 2005). Peripartum, the mother mobilizes these lipophilic contaminants from her fat reservoirs and eliminates them via milk (Fig. 3A) such that the transgenerational exposure of the calves lasts until weaning.

3.2.4.1. Calf body levels at birth. To quantify prenatal POP exposure, calf blood serum was collected before colostrum ingestion (Figure S9B; Tables S22-23) (Hirako, 2008b), resulting in concentrations 1.5-fold higher compared to the cows. The first adipose tissue sample, however, was taken at DIM89, since the calves were very lean after birth (Fig. 3C, Tables S20-21). Nevertheless, it was possible to determine the perirenal adipose tissue concentration of the deceased one-week-old exposed calf, showing levels of 28 ng iPCBs and 6.5 pg dlPCB + PCDD/F TEQ g_{lipids}^{-1}. These levels were 3.0- and 2.2-fold lower compared to the other exposed calves serum but remarkably close to the adipose tissue of the exposed cows at DIM1.

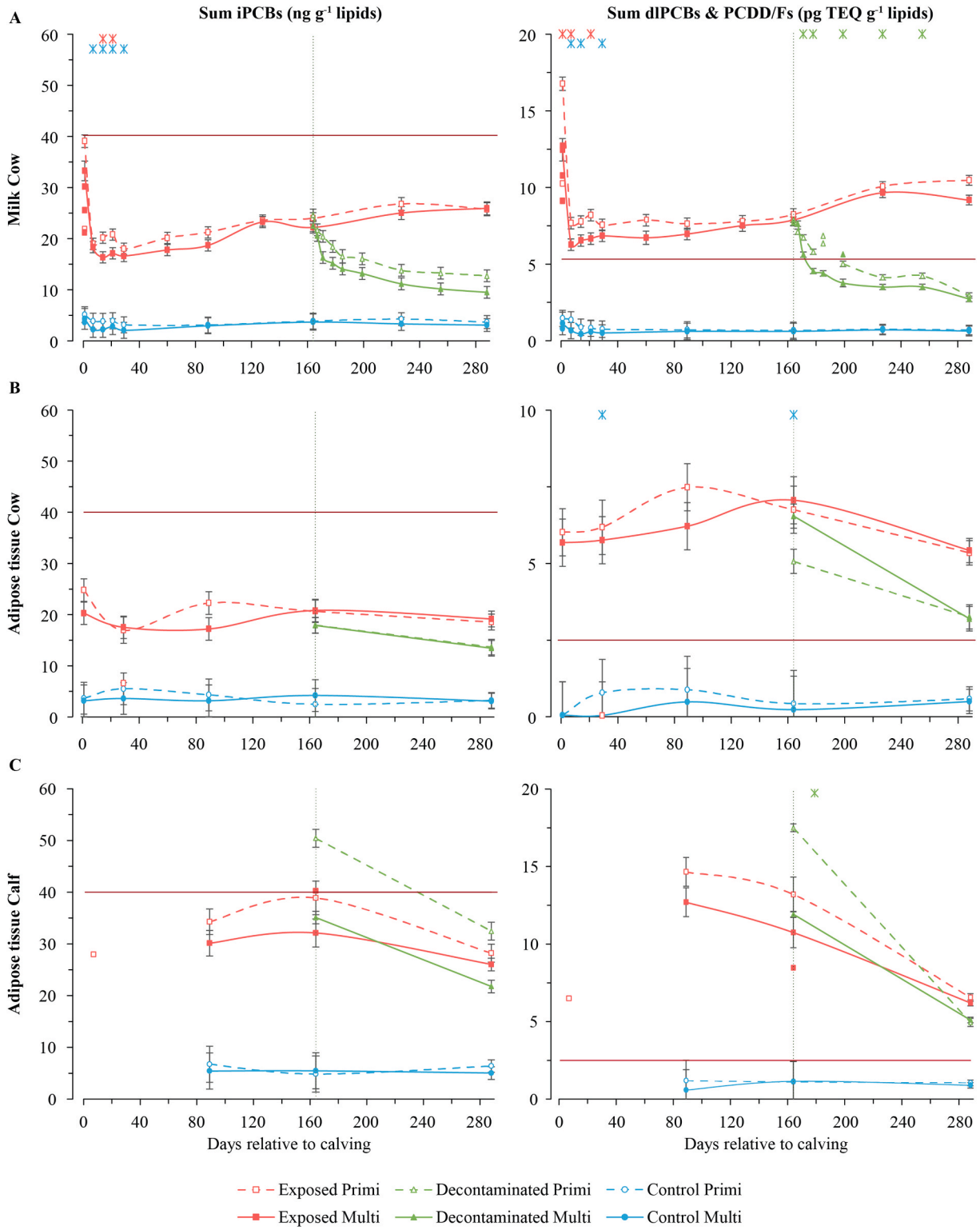

Fig. 3. Dynamics of the lower bound concentration for the sum of the iPCBs (left panels), and dlPCBs and PCDD/Fs (right panels) in cow milk (A), cow adipose tissue (B), and calf adipose tissue (C). The latter includes the deceased one-week-old exposed calf. The vertical dotted line at DIM164 indicates the initiation of decontamination. The red horizontal line represents the EU's maximum regulatory level in milk (A) and adipose tissue (B and C; Regulation (EU) Nr. 1259/2011). Least squares means and standard errors are displayed. Exposed primiparous animals: for cows $n = 4$ until DIM164 and $n = 2$ thereafter; for calves $n = 4$ until DIM89, $n = 2$ from DIM89 until 164, and $n = 1$ thereafter. Exposed multiparous animals: for cows and calves $n = 4$ until DIM164 and $n = 2$ thereafter. Decontaminated primiparous animals: for cows $n = 2$ and for calves $n = 1$. Decontaminated multiparous, control primi- and multiparous animals: for cows and calves $n = 2$. Measurements out of order were represented as separate points. Significant differences between parities at the corresponding time point are indicated as $^*P < 0.05$. Exposed and decontaminated groups were always significantly different from the control group ($P < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

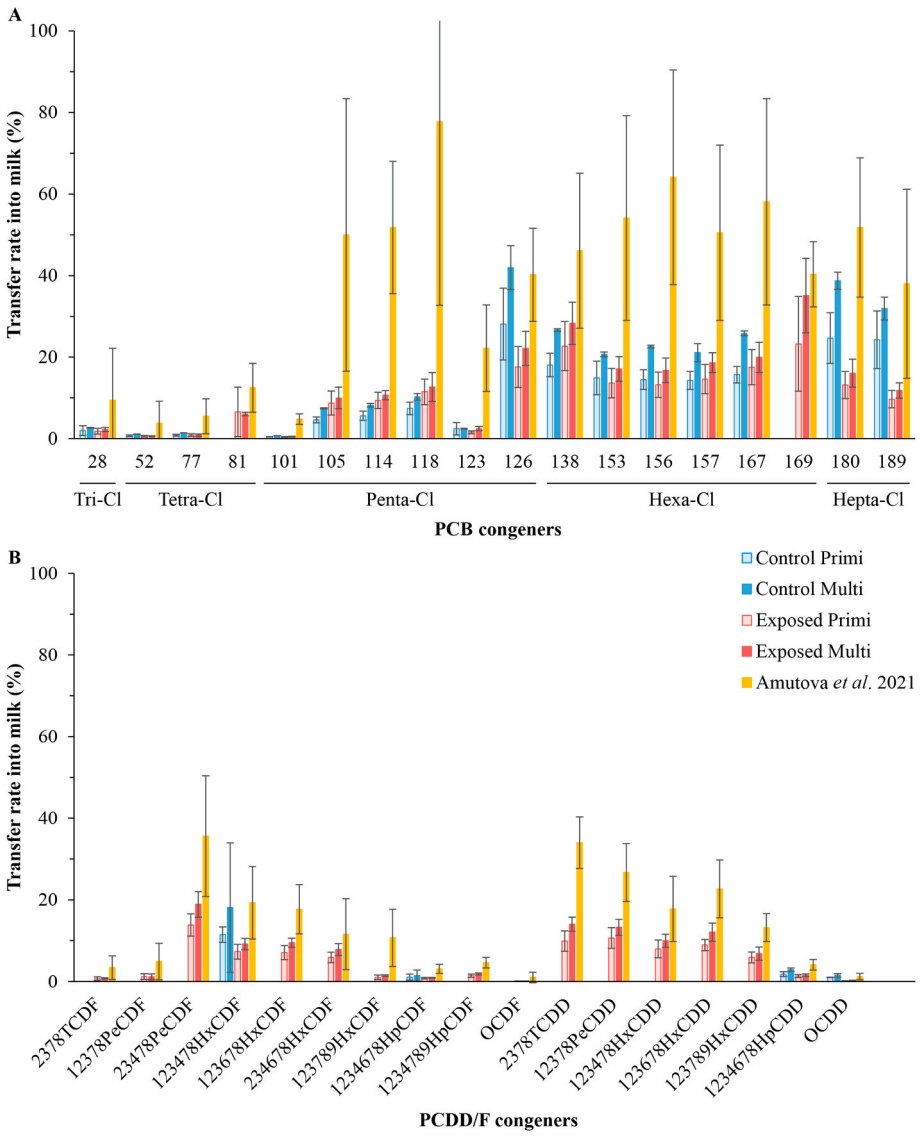

Fig. 4. Transfer rates of PCB and PCDD/F congeners in the present study and meta-analysis means from dairy cattle studies (Amutova et al., 2020). Least squares means and standard deviations for DIM164 are reported. For exposed primi- and multiparous cows: $n = 4$; and for control primi- and multiparous cows: $n = 2$. The nested effect Parity(Treatment) at DIM164 was significant ($P < 0.05$) for control PCB156, whereas a trend ($P < 0.10$) was seen for control PCB138 and PCB157.

3.2.4.2. Effects of dietary treatments and calf physiology (parity of the mother and lactation stage). Independent of dietary treatment, the highest iPCB concentration in blood serum was found at birth (29 ± 6.6 and 84 ± 4.6 ng g_{lipids}^{-1} for control and exposed calves, respectively) and declined by 2.5-fold within one month ($P < 0.05$). Later, iPCB concentration in blood serum remained stable for control calves and exposed multi-calves ($P > 0.05$). Concentrations of dlPCB + PCDD/F in blood serum of exposed calves decreased 2.5-fold from birth (14 ± 1.5 pg TEQ g_{lipids}^{-1}) to slaughter, whereas for control calves, it remained stable (0.97 ± 0.99 pg TEQ g_{lipids}^{-1} at birth, Figure S9B). The adipose tissue time trend paralleled that of blood serum, with iPCB concentrations 1.4-fold and dlPCB + PCDD/F 2.1-fold lower than the blood serum (Fig. 3C).

The exposed primi-calves showed higher POP concentrations in blood serum and adipose tissue over time compared to the multi-calves (significant for blood serum iPCBs, $P < 0.05$). This might seem contradictory as the multi-calves generally have a higher POP intake than primi-calves, except for DIM1 (Table S5). However, this results from the higher milk energy intake of multi-calves, which explains their higher growth rate and consequent higher BW (Fig. 2), showing that multi-calves could dilute POPs better than primi-calves. This difference in concentration between primi- and multi-calves vanished at the end of lactation due to a decrease in milk intake and, thus, exposure difference (ng d^{-1} kg^{-1} BW) over time.

3.2.4.3. Effects of transgenerational transfer (cow-calf comparison). The calves' blood serum iPCB concentrations were 1.5-fold higher compared to the cows' at DIM1 and 288, with even higher differences mid-lactation (2.3-fold at DIM89 and 164). Concentrations of dlPCBs + PCDD/Fs also increased further during suckling, but at DIM288, the pattern reversed with 1.4-fold higher levels in cows compared to calves (Tables S18, S23). In adipose tissue, iPCB and dlPCB + PCDD/F concentrations in exposed calves were 1.7- and 1.9-fold higher, respectively, at DIM89 and 164 compared to cows' levels. Toward DIM288, this difference decreased to 1.4- and 1.2-fold, respectively. Indeed, from DIM164 to 288, adipose tissue iPCBs and dlPCBs + PCDD/Fs in calves decreased by 1.3- and 1.9-fold, respectively, compared to only 1.1- and 1.3-fold in cows (Fig. 3B and C, Tables S16, S21). This faster decrease in concentrations in calf adipose tissue resulted from the progressively lower POP-exposure (POP intake per kg BW decreased 1.7-fold) and the

concomitant increase in body dilution space (BW increased 1.7-fold and adipose cell size 1.3-fold; Table S5). Such trends explain why, in monitoring plans, young suckling calves (3–6 months) were found to be more prone to having higher POP concentrations compared to older calves (≥10 months) or their mothers (BVL, 2011).

3.3. PCB and PCDD/F decontamination kinetics

Decontamination in cow's milk is generally investigated by depleting concentrations, resulting in a biphasic elimination profile (Fig. 3A). As seen in this study, there is generally an initial short-term phase (α) with a rapid decline in concentration, which is followed by a long-term phase (β) characterized by a slow elimination rate (Table 1) (Tuinstra et al., 1992).

For some congeners, no half-lives could be determined. A too-flat elimination curve was seen for PCB114 and 2378TCDD, while an extremely rapid short-term phase was registered for OCDF, which has previously been reported (Huwe and Smith, 2005). Others showed no differences in milk concentrations between treatments and over time (PCB52, 101, 123), presumably due to a high metabolization rate (Mclachlan, 1993), as they only contribute 0.1–5% to the total milk concentration with low TRs as described previously (Fig. 4A).

3.3.1. Effects of cow physiology (parity and lactation stage)

Overall, in primiparous cows, PCBs had higher α and β half-lives than in multiparous cows, which is in accordance with previous observations (Harrison et al., 1996; Huwe and Smith, 2005). This suggests that higher milk fat yields entail faster PCB elimination through milk excretion, and lower half-lives. In addition, primiparous cows showed a larger body fat accretion over the last four months of lactation compared to multiparous cows, as indicated by adipose tissue cell size and thickness dynamics. Body fat mass could be an additional interference, since a smaller volume of dilution in multiparous cows might lead to faster elimination from adipose tissue to milk (Tuinstra et al., 1992).

In primiparous cows, milk PCDD/F concentrations showed a stronger decline, resulting in shorter half-lives ($t_{1/2}\alpha$ = 3.0 and $t_{1/2}\beta$ = 78 d), compared to dlPCBs (Huwe and Smith, 2005). However, the multiparous cows displayed, against expectations, higher α and β half-lives of 6.0 and 262 d, respectively.

For the decontamination kinetics in cow blood serum, no biphasic exponential decay model could be fitted, since the sampling started only 35 d after starting decontamination (Figure S9A; Table S18). However, blood serum decontamination kinetics broadly mirrored milk kinetics, which suggests comparable decontamination kinetic parameters for the closely connected compartments. This is in accordance with PCB observations in dairy goats (Fournier et al., 2013). For both milk and blood

Table 1
Short-term (α) and long-term (β) half-lives (in days) for iPCBs, dlPCBs, and PCDD/Fs in cow milk in the present and previous studies.

Experiment	Present study Primi		Present study Multi		Huwe and Smith (2005)		Olling et al. (1991)	Tuinstra et al. (1992)
No. of animals	2		2		1		3	4
Lactation	During decontamination 5.9 kg_{milk} d^{-1} (2997 kg entire lactation)		During decontamination 9.7 kg_{milk} d^{-1} (4243 kg entire lactation)		Decontamination started at DIM224 (25.2 kg_{milk} d^{-1} during exp.)		Decontamination started at DIM120-180	Decontamination started at DIM1 (22.8 kg_{milk} d^{-1} during exp.)
Decontamination time	124 d		124 d		40 d		93 d	100 d
	$t_{1/2}\alpha$	$t_{1/2}\beta$	$t_{1/2}\alpha$	$t_{1/2}\beta$	$t_{1/2}\alpha$	$t_{1/2}\beta$	$t_{1/2}\beta$	$t_{1/2}\beta$
iPCBs								
PCB138	12.2	564	4.6	188				
PCB153	7.6	311	4.8	170				
PCB180	4.9	290	4.7	209				
Sum	7.7	317	4.7	183				
dlPCBs								
PCB105	8.3	894	6.4	327				
PCB118	4.4	291	2.5	205				
PCB126	7.8	216	6.4	189	10.7	196		
PCB156	5.8	510	2.0	194				
PCB157	6.0	373	1.7	189				
PCB167	6.9	259	2.3	290				
PCB169					1.5	39		
PCB189	2.9	237	3.5	245				
TEQ min	7.6	231	6.2	202	6.1	87		
PCDD/Fs								
2378TCDF							0.8	
23478PeCDF			5.9	175	4.6	43	49	63
123478HxCDF	8.3	178	4.9	196	4.4	51	49	69
123678HxCDF	1.2	91	3.5	130	3.3	35		86
234678HxCDF			11.8	598	4.1	41		92
1234678HpCDF					4.9	46	34	88
1234789HpCDF								55
OCDF					0.1	14		
2378TCDD							40	59
12378PeCDD			3.1	149	4.1	51	43	63
123478HxCDD	15	478	7.8	116	5.4	46		126
123678HxCDD	0.9	110	3.2	143	3.8	36	48	159
123789HxCDD	1.5	62	4.2	102	4.0	42		97
1234678HpCDD					15	54	27	
OCDD					0.2	73		63
TEQ min	3.0	78	6.0	262	4.7	62		

For PCB28, 81, 169, 2378TCDF, 12378PeCDF, 123789HxCDF, and OCDD no $t_{1/2}$ could be determined due to milk concentrations lower than the LOQ. DIM: days in milk.

serum, after 124 d of decontamination, it was found that concentrations were still higher than in control cows ($P < 0.05$).

3.3.2. Effects of transgenerational transfer (cow-calf adipose tissue comparison)

Decontamination was also visible in cow and calf adipose tissue (Fig. 3B and C, Tables S16, S21). In adipose tissue, POP concentration decreased in decontaminated and exposed animals, although this effect was less pronounced in the latter. Concentrations of iPCBs and dlPCBs + PCDD/Fs decreased from DIM164 to 288 1.1- and 1.3-fold in exposed cows, and 1.3- and 1.8-fold in decontaminated cows, respectively. In exposed primi- and multi-calves, concentrations of iPCBs decreased 1.4- and 1.2-fold compared to 1.6- and 1.6-fold in decontaminated calves, respectively. Concentrations of dlPCBs + PCDD/Fs in the adipose tissue of exposed primi- and multi-calves decreased 2.0- and 1.7-fold, and 3.5- and 2.3-fold in decontaminated calves, respectively.

Such faster decreases in calf compared to cow adipose tissue seemed to be independent of changes in POP intake when moving from exposed to control diets. The daily dose per kg BW of decontaminated calves from DIM164 to 288 decreased 7.5-fold for iPCBs and 9.8-fold for dlPCBs + PCDD/Fs. For cows, it decreased 4.7- and 40-fold, respectively. These results suggest that, during the suckling period, the adipose tissue decontamination potential through growth dilution (i.e., increase in POP storage pool lipid mass) observed in calves is stronger than the milk production and subsequent excretion observed in cows, as previously outlined in a comparison of primiparous suckling cows and calves (Rychen et al., 2011). This was also observed when computing half-lives in the adipose tissue of the calves and cows, based on a one-compartment model (data not shown, as it is based on only two time points). The calf adipose tissue half-lives were lower for each congener than in cows. However, after weaning, when the growth rate decreases, this dilution effect in calves may progressively vanish.

4. Conclusion

This study greatly enhanced the understanding of PCB and PCDD/F transgenerational transfer from the diffusive soil source to food-producing ruminants, which is essential to ensuring chemical food safety and the sustainability of livestock systems. It was demonstrated that the accumulation potential of different PCB and PCDD/F congeners in low-yielding cows and calves depends on their physicochemical properties, which is consistent with the persistency rankings of previous dairy cow studies. If the ingested dose is known, TRs can facilitate the prediction of levels in food products, such as milk. However, parity and lactation stage, which are linked to differences in milk fat yield and forage intake, have to be considered, as these factors influence TRs. The lower the milk fat yield, the lower the TR seemed to be, which lead to the reduced elimination rate seen in the prolonged 2-phased half-lives. The transgenerational transfer occurred via placenta and suckling, resulting in 2-fold higher adipose tissue and blood serum POP concentrations in young calves (1–6 months old). However, their increase in body fat mass, as well as reduction in milk intake over time, led to an efficient dilution of POPs in both the decontaminated and exposed calves, which reached concentrations in adipose tissue comparable to their mothers' at the end of lactation. It would be of interest to quantify the POP distribution among different tissues and set up a mass balance to characterize the POP fraction not transferred to milk but metabolized, excreted through feces, or stored in the body. These results would be of great value to researchers evaluating or improving existing physiological-based toxicokinetic models (Bogdal et al., 2017); so that these models can be applied in risk assessment to ensure safe food products by calculating e.g., needed growing periods.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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