Transfer of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) and polychlorinated biphenyls (PCBs) from oral exposure into cow's milk – Part I: state of knowledge and uncertainties

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Abstract

Polychlorinated dibenzo-*para*-dioxins (PCDDs) and dibenzofurans (PCDFs) (collectively and colloquially referred to as 'dioxins') as well as polychlorinated biphenyls (PCBs) are persistent and ubiquitous environmental contaminants that may unintentionally enter and accumulate along the food chain. Owing to their chronic toxic effects in humans and bioaccumulative properties, their presence in feed and food requires particular attention. One important exposure pathway for consumers is consumption of milk and dairy products. Their transfer from feed to milk has been studied for the past 50 years to quantify the uptake and elimination kinetics. We extracted transfer parameters (transfer rate, transfer factor, biotransfer factor and elimination half-lives) in a machine-readable format from seventy-six primary and twenty-nine secondary literature items. Kinetic data for some toxicologically relevant dioxin congeners and the elimination half-lives of dioxin-like PCBs are still not available. A well-defined selection of transfer parameters from literature was statistically analysed and shown to display high variability. To understand this variability, we discuss the data with an emphasis on influencing factors, such as experimental conditions, cow performance parameters and metabolic state. While no universal interpretation could be derived, a tendency for increased transfer into milk is apparently connected to an increase in milk yield and milk fat yield as well as during times of body fat mobilisation, for example during the negative energy balance after calving. Over the past decades, milk yield has increased to over 40 kg/d during high lactation, so more research is needed on how this impacts feed to food transfer for PCDD/Fs and PCBs.

Key words: Food safety: Transfer parameters: Ruminants: Carry-over

Introduction

The term 'dioxins' is colloquially used for a group of highly toxic organochlorine compounds consisting of seventy-five poly-chlorinated dibenzo-*para*-dioxins (PCDDs) and 135 polychlori-nated dibenzofurans (PCDFs) differing in number and position of benzylic chlorine atoms. They arise as unintentional industrial by-products of, for example, waste incineration, cement works or metal industry and are formed to a lesser degree during forest fires and volcanic eruptions[1–3].

Another type of organochlorine compound is represented by the group of polychlorinated biphenyls (PCBs) consisting of 209 congeners, each differing in position and number of chlorine atoms. Because of their useful properties, such as flame retard-ancy and electrical insulating capacity, they were industrially produced beginning in the 1930s[4]. Popular brands of PCB mix-tures in the past included Aroclor, Chlophen and Kanechlor, which were commonly produced until their production was banned. The total worldwide production of PCBs is estimated

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to have been 1·3–1·4 million metric tonnes[5]. Despite the ban on intentional production, unintentionally formed PCBs were recently found in paint colourants[6] and polymers such as silicones[7]. Furthermore, PCDD/Fs and PCBs are unintentionally formed in many combustion processes[8].

Among PCBs, twelve congeners are referred to as dioxin-like PCBs (dl-PCBs) owing to their molecular conformational and toxicological similarity to dioxins. The remaining PCBs exhibit different toxicological properties and are therefore labelled non-dioxin-like PCBs (ndl-PCBs). From an analytical perspective, detailed full-congener ndl-PCB measurements are time consuming and expensive. Therefore, six of these ndl-PCBs (Ballschmiter congener identification numbers 28, 52, 101, 138, 153 and 180[9]) are used as indicator ndl-PCBs for risk assessment purposes[10]. These six indicator ndl-PCBs represented approximately 50% of the total ndl-PCB content in food samples, and at least one of the six indicator ndl-PCBs was quantified in 68·4% of feed and 82·6% of food samples[11].

Both PCDD/Fs and PCBs are highly lipophilic and extremely stable compounds, with environmental degradation half-life periods up to several decades[12]. Once released, they persist in the environment, undergo transport and may end up in foods of animal origin mainly via contaminated feed and ingested soil[13]. PCDD/Fs and PCBs are still considered one of the main contaminants in the food chain[14]. Owing to their lipophilic properties, organochlorine chemicals undergo bioaccumulation, especially in fatty tissues and other fat-containing foods[15]. Owing to their ubiquitous occurrence, human exposure to PCDD/Fs and PCBs is inevitable, particularly through foods of animal origin, including 'milk and milk products'[16]. Understanding the dynamics of feed to food transfer[17] (historically also called 'carry-over') of these contaminants is thus crucial to perform appropriate health risk assessment.

Chronic and high exposure to PCDD/Fs and dl-PCBs can induce endocrine and reproductive interferences[18], impair immunological reactions and cause developmental disruption as well as cancer[19]. Nevertheless, the most sensitive effect (i.e. the effect occurring at the lowest dose in the most sensitive population) is related to a reduction in sperm concentration for people exposed in early years[20]. The effects that PCDD/Fs and dl-PCB have on human health result mainly from the toxic activation of the aryl hydrocarbon receptor (AhR)[21]. AhR influences numerous metabolic pathways[22]. Of all possible congeners, only seven PCDDs, ten PCDFs and twelve dl-PCBs can bind to the AhR[23], making these compounds very relevant for research and risk assessment. The toxicological potency of these twenty-nine congeners is based on 2,3,7,8-TCDD, also known as Seveso-Dioxin, which is the lead compound with the highest toxicity of this group. According to the congener-specific toxicity relative to 2,3,7,8-TCDD, toxic equivalency factors (TEF) were derived to ease toxicological risk assessment. Internationally, TEFs for PCDD/Fs were defined by NATO/CCMS in 1988 as I-TEF and for PCDD/Fs and dl-PCBs by the World Health Organization (WHO) in 1997[24,25]. The WHO TEFs were again revised in 2005[26]. Using the TEF concept, the concentration of the different congeners can be summarised as toxicity-weighted masses or toxic equivalent (TEQ), which is used for risk assessment in feed and food worldwide as well as in

management measures (i.e. the setting of maximum levels/content in food and feed). Owing to their toxicological properties, WHO International Agency for Research on Cancer (IARC) has listed 2,3,7,8-TCDD, 2,3,4,7,8-PeCDD and PCB-126 in Group 1 as 'carcinogenic to humans'[27]. Furthermore, the international Stockholm Convention on Persistent Organic Pollutants (2001) lists intentionally and unintentionally produced PCDD/Fs and PCBs as part of the so-called dirty dozen, a compilation of persistent organic pollutants known to cause adverse effects in humans and the environment[28].

The toxicity of non-dioxin-like PCBs (ndl-PCBs) cannot be summarised through the interaction with a single receptor. Adverse effects on the thyroid, liver and brain biochemistry, immunotoxicity, oestrogenicity, reproductive and neurodevelopmental effects were reported in laboratory animals after exposure to ndl-PCBs[29]. Since ndl-PCBs are frequently accompanied by PCDD/Fs and dl-PCBs, as well as other toxic compounds, establishing an unequivocal congener-specific toxicological profile is not straightforward[30].

In addition to the inevitable environmental background levels, recurrent contamination incidents with PCDD/Fs and PCBs have affected the safety of foods of animal origin during the past decades[31]. The first reported food chain incident occurred in the 1950s in the United States, where thousands of chickens died of 'chicken-oedema-disease', caused by diets containing PCDD/F-contaminated fat[32,33]. Also in recent times, feed and food incidents have occurred frequently with different sources of the PCDD/Fs and PCBs. For example: contaminated fat intended as feed material in Belgium[34], contaminated citrus pulp from Brazil causing elevated PCDD/F levels in European milk products[35], bakery waste used as animal feed in Germany contaminated during the drying process[36], German beet pulp contaminated during the drying process leading to elevated milk levels in the Netherlands[13], choline chloride premix in animal feed contaminated with PCDD/Fs and PCBs by pine saw dust[37], flooding of the river Elbe and subsequent contamination of flooded grazing areas in 2003[38], recycled feeding fat from gelatine production contaminated by a broken filter[39] and the Irish dioxin case in 2008 caused by PCB containing fuel used to dry animal feed, which led to the culling of 5707 cattle and 170 605 pigs[40]. As suggested above, many of these feed and food incidents affected cattle[41–43], leading to elevated PCDD/F and dl-PCB levels in the milk. This is particularly concerning, as a bulk of the PCDD/F and PCB contamination in humans stems from the consumption of milk and milk products[16,44]. Each source of PCDD/Fs and PCBs is associated with characteristic congener patterns that can be used to forensically relate contamination incidents and infer their possible sources[14]. However, it should be noted that passage through the animal alters the original source congener pattern in a way that can be predicted using congener-specific toxicokinetic models.

To protect the consumers, organisations such as the European Commission have defined action and maximum levels for the PCDD/F and dl-PCB content as well as maximum levels for ndl-PCB content in different animal feed and foods[45–47]. Following the risk-assessment-derived tolerable weekly intake of 2 pg WHO-PCDD/F-PCB-TEQ/(kg body weight × week)[16], maximum levels might be revised (i.e. lowered) in the near

future. Although emissions of PCDD/Fs have declined by 45% between 1990 and 2012 in the European Union[48], our understanding of their toxicology has led to lower TWIs, meaning that they remain an important group of contaminants for research and regulation. Exceedance of maximum levels leads to non-marketable food and feed products. In the case of contamination of cattle feed and subsequent contamination of milk, the length of the depuration period depends on the initial intake and on the daily output via milk. In a case described by Malisch *et al.*[35], this depuration period may take 1 year before reaching levels below maximum levels. Consequently, the resulting milk may not be marketable for a long period of time, resulting in considerable economic damages[49]. To improve the risk management of recurrent PCDD/F and PCB incidents, reliable data and models on the transfer behaviour of all toxicologically relevant congeners are needed. In the case of contaminated animal feed, knowledge about the transfer of these congeners from feed to milk is necessary to estimate the extent of milk contamination. In the case of a contamination event, information about the elimination kinetics including the half-life of the congeners is indispensable to predict the length of the depuration period needed for the cow's milk concentrations to fall below legally binding maximum levels.

Since the 1970s, many studies have analysed the transfer of organochlorines, specifically PCDD/Fs and PCBs from feed to milk, which have been partly reviewed elsewhere[50–55]. Since the early 1990s, attempts have been made to develop toxicokinetic models to quantitatively predict the transfer of different congeners into milk, which is discussed in detail in part II of this review[56]. However, no in-depth comparison of data and knowledge in terms of their applicability to risk analysis has yet been made. In this review, seventy-six studies and secondary literature on this topic were evaluated with a focus on the quality and usability of the results for risk assessment. The main goals of the review are:

- evaluate the availability of transfer parameters (such as transfer rates and elimination half-lives) for all toxicologically relevant congeners (seven PCDDs, ten PCDFs, twelve dl-PCBs) as well as the indicator ndl-PCBs in terms of their applicability for risk assessment;
- identify future research focus areas regarding missing data with respect to the factors that influence transfer, for example metabolic status and breed.

Variability of experiments and reports on the transfer of PCDD/Fs and PCBs into milk

For this review, seventy-six experimental and theoretical studies from the past 50 years, as well as twenty-nine secondary literature items on the transfer of PCDD/Fs and PCBs into milk of ruminants, were consulted. The complete dataset is compiled in machine-readable form as Supplementary Materials Part B. In these studies, various experimental approaches were followed to derive kinetic parameters to describe the feed to milk transfer. We present an overview of the variability between the studies in terms of exposure scenarios, animal breeds (Table 1)

Table 1. Cattle breeds identified in the various transfer studies

References	Animal breed	Animal usage
(35,42,57–69)	Dairy cattle	Dairy
(70–82)	Holstein cows	Dairy
(41,83,84)	Holstein Friesian	Dairy
(85)	English Holstein Friesian	Dairy
(86)	Italian Holstein Friesian	Dairy
(87–94)	German Holstein	Dairy
(95–98)	Jersey	Dairy
(99,100)	Angler	Dairy
	German Red Pied	
	German Black Pied	
(61,101–105)	Fries Holland	Dairy
(106,107)	Guernsey	Dairy
(108)	Brown Swiss	Dairy
(109–114)	Simmental	Dual purpose
(43,115)	Simmental cross breeds	Dual purpose
(61,116)	Meuse-Rhine-Issel	Dual purpose
(117)	Beef cattle	Beef
(118)	Aberdeen Angus	Beef
	German Angus – Blonde d'Aquitaine cross breeds	
(119)	Hereford	Beef
(70,120–123)	Unknown	Unknown

and data integrity and how these differences influence the comparability and our choice of studies.

Exposure scenarios in dairy cattle

Regarding the basic experimental design, the studies can be classified into field, incident, controlled feeding and mass balance studies. In field studies, in a stable or on pasture, the daily intake of contaminants could be assumed as being steady, but especially for grazing animals, this assumption is uncertain. Incidents and case reports refer to short-term contamination events where the origin and extent of the exposure may be uncertain.

In controlled feeding studies, the daily amount of contaminant uptake is known; contaminants are either spiked into the daily ration or they are already present in known amounts, with the total feed intake recorded. Alternatively, they are applied as a bolus (e.g. gelatine capsule) into the rumen. The time of exposure in feeding studies varied from 1 d[62,75,79,80,87,88,95,97,98,102,103,120,124–126] to several weeks (<28 d)[60,77,78,98,113] (Table 2). In some feeding studies, the animals were exposed to PCDD/Fs and PCBs during their dry period[61,88,91,93,94,100,114,115,119]. Since elimination via lactation is not possible in this case, PCDD/Fs and PCBs accumulate in the gravid cows' body fat – and likely in the unborn foetus[127]. Mass balance studies are a subcategory of feeding studies in which feed of a known contaminant concentration (background or higher) is given over a prolonged time of several weeks, with the intention of approaching a steady state between contaminant intake and elimination through milk and other excretion pathways[65–68,72,73,109–111,113,114,128]. Furthermore, the transfer of contaminants into milk has been studied after intravenous[120] and intramuscular[125] applications. The dose of PCDD/Fs and PCBs administered in feeding studies has decreased since the 1970s, likely driven by improvements in analytical detection capabilities (e.g. limit of quantification).

Table 2. Studies used in assessment of transfer rates (TR), transfer factors (TF) and biotransfer factors (BTF) from feed to cow milk in chronological order

Main reference	Secondary reference	Study type	Animal breed	Number of animals	Exposure time (d)	Analytes	Transfer parameters
Firestone et al., 1979[76]	(72,129,130)	Feeding	Holstein	3	70	PCDD	TR, TF, BTF
Tuinstra et al., 1981[57]	(88,111,130)	Feeding	Dairy Cattle	6	56*	ndl-PCB	TR, TF, BTF
Heeschen et al., 1986[87]	(110,130)	Feeding	German Holstein	3	63*	ndl-PCB	TR, BTF
Ewers, 1987[88]	(89,131,132)	Feeding	German Holstein	6	56*	ndl-PCB	TR, TF
Ewers et al., 1989[90]		Feeding	German Holstein	3	28	ndl-PCB	TR
Jilg et al., 1992[112]		Feeding	Simmental	4	133*	PCDD/F	TR
McLachlan, 1992[110]	(109,111,130)	Feeding	Simmental	1	36	PCDD/F, dl-/ndl-PCB	TR, BTF
Ruoff, 1995[91]	(133,134)	Feeding	German Holstein	10	67–125	PCDD/F	TR
McLachlan and Richter, 1998[113]	(130,135)	Mass balance	Simmental	4	91*	PCDD/F	TR, TF
Fries et al., 1999[72]	(128,135)	Mass balance	Holstein	4	58	PCDD/F	TR, TF, BTF
Thomas et al., 1999[66]	(65,130,135)	Mass balance	Dairy cattle	5	109	dl-/ndl-PCB	TR, TF, BTF
Winters et al., 2000[68]	(67,135)	Mass balance	Dairy cattle	2–4	135	PCDD/F	TR, TF, BTF
Fries et al., 2002[73]		Mass balance	Holstein	2–4	28–58	PCDD/F	TR
Huwe and Smith, 2003[82]	(135)	Feeding	Holstein	1	40	PCDD/F, dl-PCB	TR
Kerst et al., 2004[106]	(107,135)	Feeding	Guernsey	26		PCDD/F, dl-PCB	TR, TF
Huwe and Smith, 2005[135]		Feeding	Holstein	2	40	PCDD/F, dl-PCB	TR, TF
Brambilla et al., 2008[41]		Incident	Holstein Friesian	1604	28	PCDD/F	TR, TF
Hoogenboom et al., 2015[83]		Feeding	Holstein Friesian	6	33	PCDD/F, dl-PCB	TR
Lorenzi et al., 2020[86]		Feeding	Italian Holstein Friesian	4	49	PCDD/F, dl-/ndl-PCB	TR
Driesen et al., 2022[114]		Feeding	Simmental	8 + 4	276+	PCDD/F, dl-/ndl-PCB	TR

* Converted from weeks to days by multiplying by 7.

Finally, at least four studies were available[136–139] where a theoretical approach was used to assess the exposure and transfer of PCDD/Fs and PCBs in dairy cattle. Although different exposure scenarios in the available studies provide limited comparability of data, all these experimental approaches have their specific advantages to gain insight into the fate of PCDD/F and PCB congeners in dairy cattle and to develop predictive models.

Cattle breeds and other ruminants

Studies that presented feed to milk transfer parameters were based on various lactating dairy cows and beef cattle. Specific cattle breeds were named in some studies, but not in all (Table 1). On the basis of their specific genetic potential, the milk yield differs between cattle breeds. Owing to breeding measures over the past decades, these performance differences have become more evident for specialised dairy cow breeds like Holstein cattle[140]. The potential influences of several breed-associated performance and metabolic parameters on the transfer of xenobiotics in milk of ruminants have already been shown in a modelling approach[141]. The authors of this study found that the elimination half-lives of xenobiotics can decrease significantly with increasing milk yield and increasing milk fat content, which was particularly evident for substances with slow liver metabolic rates. But, to date, no systematic study has been carried out to evaluate a potential influence of dairy cattle breed on PCDD/F and PCB transfer.

The extrapolation of the data from previous studies with lower milk-yield breeds to high-performance dairy cows needs to be addressed in the future and should be adopted in toxicokinetic models. In addition, the transferability of data might be further limited by other factors such as metabolic state, body weight and body fat content as well as milk and milk fat production, and will be discussed below.

In addition to cattle, studies have also been carried out with other ruminants, including dairy sheep[125], dairy goats[120,124,126,142–148] and dairy buffaloes[149]. While the milk fat content of goats is very similar to that of cattle, it is more than twice as high in the milk of sheep and buffalo[150]. Regarding the lipophilic properties of PCDD/Fs and PCBs, these different milk fat contents could influence the transfer rates from feed to milk. Even though there are currently no experimental data available on this aspect, the composition of milk should be considered comparing transfer data in different ruminant species. Furthermore, Rychen et al. (2008) hypothesised goats to be a valuable 'lactating animal model' with a transfer behaviour of PCDD/Fs into milk similar to cows[52]. Therefore, the aforementioned studies on goats will be referenced in the following if appropriate.

Data integrity

A crucial point in evaluating and comparing transfer studies is how and what data were published, as well as how to handle ambiguous or missing data. This is especially important when essential data for transfer modelling, such as milk and milk fat yields, are not reported. Furthermore, data expression in a variety of units and dimensions makes harmonisation challenging. Most studies expressed the amount of PCDD/F and PCB on

the basis of milk fat corresponding to regulatory maximum residue levels or daily excretion via milk. However, in some studies the amount was expressed on a whole milk basis[77,95,98,115,142,151], not necessarily providing information about the respective milk fat content.

Another important aspect of data integrity is the length of the exposure period. During the initial first weeks of exposure, contaminant levels in milk fat increase rapidly, while after weeks of exposure, the increase flattens to slowly approach a steady state. Transfer parameters calculated at the end of a short exposure period will lead to an underestimation compared with steady-state or near-steady-state values. With a constant intake of PCDD/Fs and PCBs, a near steady state was postulated in lactating cows after 17 and 21 d for PCDDF and PCB TEQs[82,135], 40–60 d for Aroclor 1254[70] and for specific congeners after 14–42 d[86], 21–28 d[89,131], 28 d[72,73], 33 d[13] and 40–70 d[134]. Predictive modelling suggested it would take approximately 150–200 d to reach a real steady state[13,42]. However, this might not be reachable owing to metabolic changes during lactation[15,41]. Therefore, an exposure period of at least 28 d is suggested for transfer studies of lipophilic persistent organic pollutants[15,141]. The time to reach steady state for PCDD/Fs and PCBs was also calculated for dairy buffaloes[149] and goats[144,146,148].

Owing to limited analytical performance and limited toxicological assessments, early studies did not differentiate between single congeners. Instead, commercially available PCB-mixtures, such as Aroclor 1254, were often used as a reference for the quantification of PCBs, and results were expressed as Aroclor 1254 equivalents[71,75,78,81,95,96,98,115,119,151]. Furthermore, some of the aforementioned studies with Aroclor 1254 were later re-evaluated to adjust for different approaches in quantification[121]. In earlier studies, another analytical challenge could have been the inefficient chromatographic performance of the available gas chromatography columns to fully separate isomers[109,110].

In literature, data for single congeners are sometimes omitted in favour of the sum of the parameters. The WHO_{2005} TEQ[26] describes our current understanding of the relative toxicity of the congeners and has its justification in risk analysis, being currently used for action and maximum levels in feed and food. Nevertheless, any future changes in the TEF for a single congener will practically invalidate entire study outcomes for which the congener-specific data are not available. Furthermore, as transfer parameters are congener specific with a wide range of variation, transfer data derived for mixtures like Aroclor 1254, or based on sum-TEQ values, are restricted to the respective congener profiles present in the contamination source. Additionally, owing to the congener-specific transfer parameters, the congener profile in milk fat is not identical to that of the source. For these reasons, future publications are advised to report congener-specific data.

Another critical point in assessing previous studies is that transfer parameters are sometimes depicted graphically but not necessarily in text or tables[72,113,122,144]. However, graphical depictions of milk fat concentrations of PCDD/Fs and PCBs during exposure and depuration could be used retrospectively to derive transfer parameters if these were not given in papers, for example Refs.[62,70,71,74,75,96,98,105,142]. For this review, we extracted data from plots using tools like the WebPlotDigitizer[152], which adds another level of uncertainty. While it is certainly possible to calculate transfer parameters from the tabulated data given in some studies[43,79,88,91,95,153], we saw those as derivative calculations and thus beyond the scope of this review. Aside from milk fat concentrations, some studies include PCDD/F and PCB concentrations in blood, faeces, body fat compartments or organs, enabling a better understanding of the kinetics, which can also be exploited with toxicokinetic modelling. On the basis of these limitations, it is clear that comparison of data from different studies is not trivial.

Kinetic parameters to characterise the feed-to-milk transfer behaviour

Studies with regard to feed-to-milk transfer of PCDD/Fs and PCBs were selected on the basis of the following criteria on study design and data quality:

- The study dealt with dairy or dual-purpose cows;
- The exposure to PCDD/Fs or PCBs was oral, and information regarding the lactation period was provided;
- The minimum exposure period was 28 d (necessary to approximate the steady state for several congeners[15,72,73,86,141]);
- The study offered congener-specific data (if other authors derived transfer parameters from the initial studies, these were also included).

Of the initial 104 primary and secondary references (of which seventy-six are primary), nineteen remained for further consideration to evaluate congener-specific feed-to-milk transfer parameters after using the above-mentioned criteria. The majority were feeding studies performed under controlled conditions (Table 2). Two further studies analysed the transfer in herds of twenty-six and 1604 animals, respectively. The first study dealt with the background contamination via fresh grass[106], while the second was a case study of a contamination incident via food supplements[41]. While daily contaminant input and feed consumption could not be as well quantified in these studies as in feeding studies, both provide average transfer parameters based on large numbers of individuals.

Exact knowledge of the contaminant exposure amount and its duration is not necessary to derive half-lives during the depuration phase. Because data on milk elimination half-lives are very limited, data from other ruminants like goats (data points marked in Figs. 4 and 5 with a red dot) were included if available (Table 3), as these are also seen as 'lactating animal models' elsewhere[52]. Whenever possible, data from individual animals instead of mean values from a group were used for plotting and discussing the transfer parameters: transfer rate, transfer factor, biotransfer factor and elimination half-lives. However, data reported as greater or smaller than a certain value were neglected. Whenever a range was reported, the arithmetic mean of the range was calculated.

Transfer rates

Transfer rates (TR), historically called carry-over rates or carry-over ratio, describe the fraction of congener intake with the diet

Table 3. Studies used in assessment of α and β elimination half-lives in milk of ruminants in chronological order

Main reference	Secondary reference	Study type	Animal breed	Number of animals	Analytes	Half-lives
Firestone et al., 1979[76]		Feeding	Holstein	3	PCDD	β
Jensen and Hummel, 1982[77]		Feeding	Holstein	2	PCDD	β
Jones et al., 1987[79]	[116]	Feeding	Holstein	3	PCDD	α
Olling et al., 1990[101]	[102]	Feeding	Fries Holland/Holstein Friesian	3	PCDD/F	β
Derks et al., 1991[104]		Field	Fries Holland/Holstein Friesian	4	PCDD/F	β
Roos et al., 1991[61]	[116]	Feeding	Fries Holland and Meuse-Rhine-Issel	4	PCDD/F	α/β
Klein, 1991[99]	[100]	Field	German Black Pied, German Red Pied Angler	20	ndl-PCB	β
Ruoff, 1995[91]		Feeding	German Holstein	3	PCDD/F	β
Malisch, 2000[35]		Incident	Dairy cattle	unknown	PCDD	β
Huwe and Smith, 2005[135]		Feeding	Holstein cow	2	PCDD/F, dl-PCB	α/β
Brambilla et al., 2008[41]		Incident	Holstein Friesian	1604	PCDD/F	β
Tremolada et al., 2014[108]		Field	Brown Swiss	unknown	dl-/ndl-PCB	β
Driesen et al., 2022[114]		Feeding	Simmental	4	PCDD/F, dl-/ndl-PCB	α/β
Foumier et al., 2013[148]		Feeding	Alpine goat	4	PCDD/F, ndl-PCB	α/β

(mass or mole) that is excreted with the milk. While TRs can be calculated for any given time period during an experiment or an incident, they reach a maximum when a steady state between constant intake and output is reached. The TR is used to assess the balances of the mass flow.

$$TR[\%] = \frac{DailyExcretionViaMilk\left[\frac{ng}{d}\right]}{DailyIntakeViaFeed\left[\frac{ng}{d}\right]} \times 100\% \quad (1)$$

Re-arranging this formula enables prediction of the daily excretion via milk for a given TR and a known daily intake via feed, that is,

$$DailyExcretionViaMilk\left[\frac{ng}{d}\right] = TR[\%]/100\% \times DailyIntakeViaFeed\left[\frac{ng}{d}\right] \quad (2)$$

This prediction from the re-arrangement of equation (1) can be seen as the simplest kind of model[154] and is only valid if the steady state has been reached and the conditions of the prediction are the same as in the determination of TR. TR is a ratio of amounts of contaminant, and is thus insensitive to the basis (e.g. dry matter for feed or milk fat for milk). Most studies expressed the transfer of contaminants into milk as TRs, and thus for all PCDD/F and PCB congeners TRs are available, as seen in the boxplot of Fig. 1. The statistical values behind this boxplot can be found in Supplementary Materials Part A, Table S1. The data used for this analysis are derived from the transfer studies listed in Table 2. Owing to differences in the reported transfer rates for the same feeding study, only the more recent parameters for PCDD/Fs and PCBs by McLachlan[109–111] were used for data analysis. We have also included transfer rates with a negative sign, such as those reported by Brambilla et al. (2008)[41] and Lorenzi et al. (2020)[86]. Although physically meaningless, a negative transfer rate can result from a background exposure correction containing measurement and other errors. Thomas et al. (1999) similarly reported a transfer rate above 100% for PCB-118, which will be discussed at a later point in this review[66].

According to this analysis, TRs of highly chlorinated ndl-PCBs and dl-PCBs are, with some exceptions, higher compared with PCDD/Fs. Altogether, congener-specific TRs lie in the range between <1% and 100%. Despite the consultation of data from comparable studies (Table 2), coefficients of variation (CV) were between 29% and 204% (Table S1), with a trend of decreasing CV at higher TRs. The wide range of calculated TRs (Fig. 1) can be due to several reasons. For instance, the data of certain studies were of low accuracy, owing to low analytical performance at lower TRs; important experimental parameters were not considered, such as contaminant source-dependent bioavailability; or the inter-individual variance between animals was very high for unknown reasons. Moreover, for several congeners, only a very limited number of studies investigating a small number of animals exist, which are thus error prone. In any case, for the purpose of modelling, the large variability in the data negatively affects the predictive power.
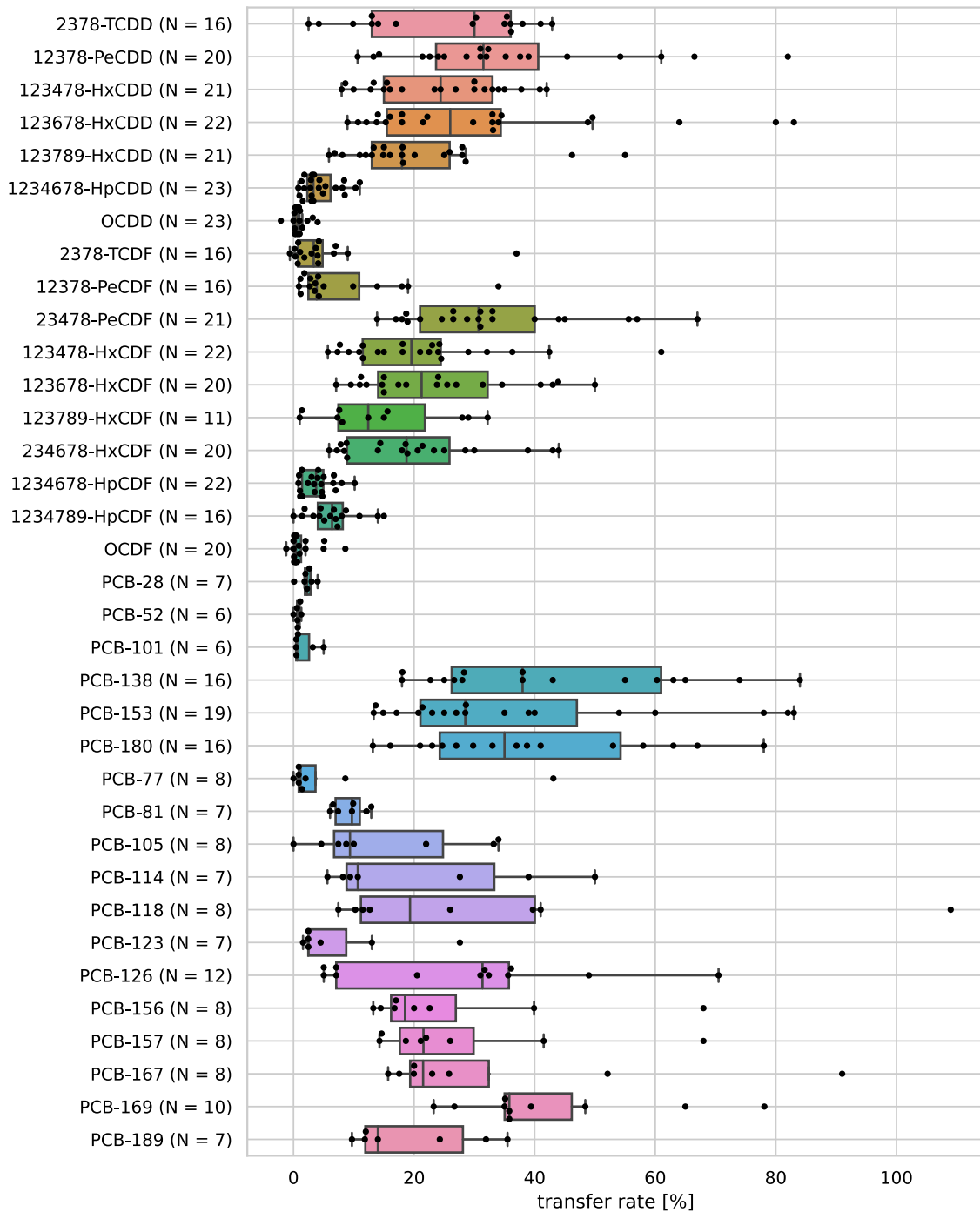
Fig. 1. Boxplots of transfer rates (TRs) for cows. Scatter points represent available data points from selected literature (refer to Table 2). Boxes ($N > 5$) are defined as the interquartile range (IQR) between 25th percentile (Q1) and 75th percentile (Q3) of the data according to the standard method. The black line in the box represents the median. Whiskers include data within 1.5 times of IQR below Q1 and above Q3. Plot generated with Python 3.10 using the Seaborn, Matplotlib, Numpy and Pandas libraries.

Transfer factors

For regulatory purposes and risk assessment, the transfer factor (TF), also known as bioconcentration factor (BCF), carry-over factor (CoF) or accumulation factor (AF), has played a key role until now. This dimensionless factor describes the quotient of the congener concentration in milk (fat) and its concentration in the feed.

$$TF = \frac{ConcentratonInMilkFat\left[\frac{ng}{kg}\right]}{ConcentrationInFeed\left[\frac{ng}{kg}\right]} \quad (3)$$

TF is a ratio of concentrations of a contaminant, and is thus dependent on the basis used. The standard basis from animal nutrition is compound feed with 88% dry matter for feed and

milk fat for milk, as used in regulatory standards. The numerical value of TF will vary if other bases are used (e.g. wet weight or just mineral components of compound feed). TF has the disadvantage of having a strong dependence on, for example, milk fat yield. Furthermore, the concept of TF can be applied to describe the transfer and storage of contaminants into fat tissue. This formula can also be re-arranged so that it can be used to predict the concentration in milk fat given concentration in feed and the TF, that is,

$$ConcentrationInMilkfat\left[\frac{ng}{g}\right] = TF \times ConcentrationInFeed\left[\frac{ng}{g}\right] \quad (4)$$

TR and TF are related through the feed efficiency (FE), or the ratio of milk fat produced per kg of feed (88% dry matter), such that:

$$TR[\%] = TF \times FE$$
$$= \frac{ConcentrationInMilkfat\left[\frac{ng}{kg}\right]}{ConcentrationInFeed\left[\frac{ng}{kg}\right]} \times \frac{milkfat\left[\frac{kg}{d}\right]}{feed\left[\frac{kg}{d}\right]}$$
$$\times 100\% \quad (5)$$

While the conversion between TR and TF is given by equation (5), the data in each study do not always allow for it to be effectively used. In this review, we have opted for only reproducing published values. TFs are less well documented than TRs. For example, there are no data given for some dl-PCBs, and for the lower chlorinated ndl-PCBs there is only one publication by Ewers (1987)[88] that calculated TFs on the basis of a study by Tuinstra et al. (1981)[57]. While Tuinstra et al. (1981) published enough data to calculate TFs, no data were given for PCB-28. It is therefore unknown how Ewers (1987) calculated the TF value, and thus this value was omitted. Furthermore, Connett and Webster (1987)[58], McLachlan et al. (1990)[109] and Huwe and Smith (2003)[82] calculated TFs on the basis of wet weight feed intake, which is not comparable to dry weight intake. Hence, these TFs were not used for further data analysis.

TFs based on studies listed in Table 2 are depicted in Supplementary Materials Part A, Table S2 and plotted in Fig. 2. The coefficient of variation of congener-specific TFs lies between 15% and 154%, again with a trend of lower CV for congeners with higher TFs. The reason for the wide range of calculated TFs (Fig. 2) may be similar to those presented above for TRs.

Biotransfer factors

Another frequently reported parameter is the biotransfer factor (BTF). Contrary to TF, and similarly to TR, it is not restricted to an exposure from a single source (e.g. feed) but can also account for contamination through multiple pathways such as air, wall paint chippings, soil, etc. BTF is a ratio of concentration in whole milk and the daily intake (dose) of a contaminant. Usually, the BTF is calculated on the basis of whole milk instead of milk fat, deviating from the standard for TF. Moreover, the BTF is

not dimensionless and has units of time/mass, such as d/kg. In non-physiological approaches (see part II of this review[56]) feed-to-milk BTFs are estimated on the basis of substance-specific octanol-water partition coefficients. However, BTF is more commonly applied in, for example, aquatic ecotoxicology (where the contaminant sources are multiple and diffuse) and is calculated as

$$BTF\left[\frac{d}{kg}\right] = \frac{ConcentrationInMilk\left[\frac{ng}{kg}\right]}{DailyIntake\left[\frac{ng}{d}\right]}. \quad (6)$$

Again, this formula can be re-arranged, so that we can predict the concentration in milk given the daily intake and the BTF, that is,

$$ConcentrationInMilk\left[\frac{ng}{kg}\right] = BTF\left[\frac{d}{kg}\right] \times DailyIntake\left[\frac{ng}{d}\right]. \quad (7)$$

When feed is the only contamination source, the BTF in whole milk basis is related to TF in milk fat basis and TR by

$$TF = BTF\left[\frac{d}{kg}\right]/FatfractionInMilk \times feed\left[\frac{kg}{d}\right] \quad (8)$$

$$TR[\%] = BTF\left[\frac{d}{kg}\right] \times milk\left[\frac{kg}{d}\right] \times 100\% \quad (9)$$

In this review, we have opted not to transform BTF into TF or TR because of incomplete reported data (since this would have required assumptions). Data on BTFs are even more sparse than for TFs, and as shown in Fig. 3, BTFs are missing for most dl-PCBs. Rosenbaum et al. (2009)[130] retroactively calculated BTFs on the basis of various studies[57,65,66,76,87,109–111,113], which were also used in the depiction of BTFs in Fig. 3. Average congener-specific BTFs given in a report by the California Office of Environmental Health Hazard Assessment[155] were omitted, as these values were based on several experimental studies[62,63,66,67,85,106,109,113,135]. The data behind Fig. 3 can be found in Supplementary Materials Part A, Table S3. The coefficients of variation varied between 22% and 140%, which is in line with the previous observations for TFs and TRs. The reasons for this variability, also apparent in Fig. 3, may be similar to those presented above for TRs.

Lastly, an appeal is presented to the next generation of risk assessors and risk managers: resist the temptation to use TF, TR and BTF as simple multiplicative factors to translate between maximum levels in food and maximum levels of contaminants in contaminated source materials (e.g. feed). Opt instead for full toxicokinetic models that capture the dynamics, physiological and metabolic variables explicitly (see part II of this review[56]). For all their disadvantages, these transfer parameters nevertheless remain a good way of comparing studies, as we do in Figs. 1–3.

Elimination half-lives

Knowledge of the elimination half-lives or rate constants is of utmost importance for risk analysis. Elimination half-lives are necessary to estimate depuration time needed to reach
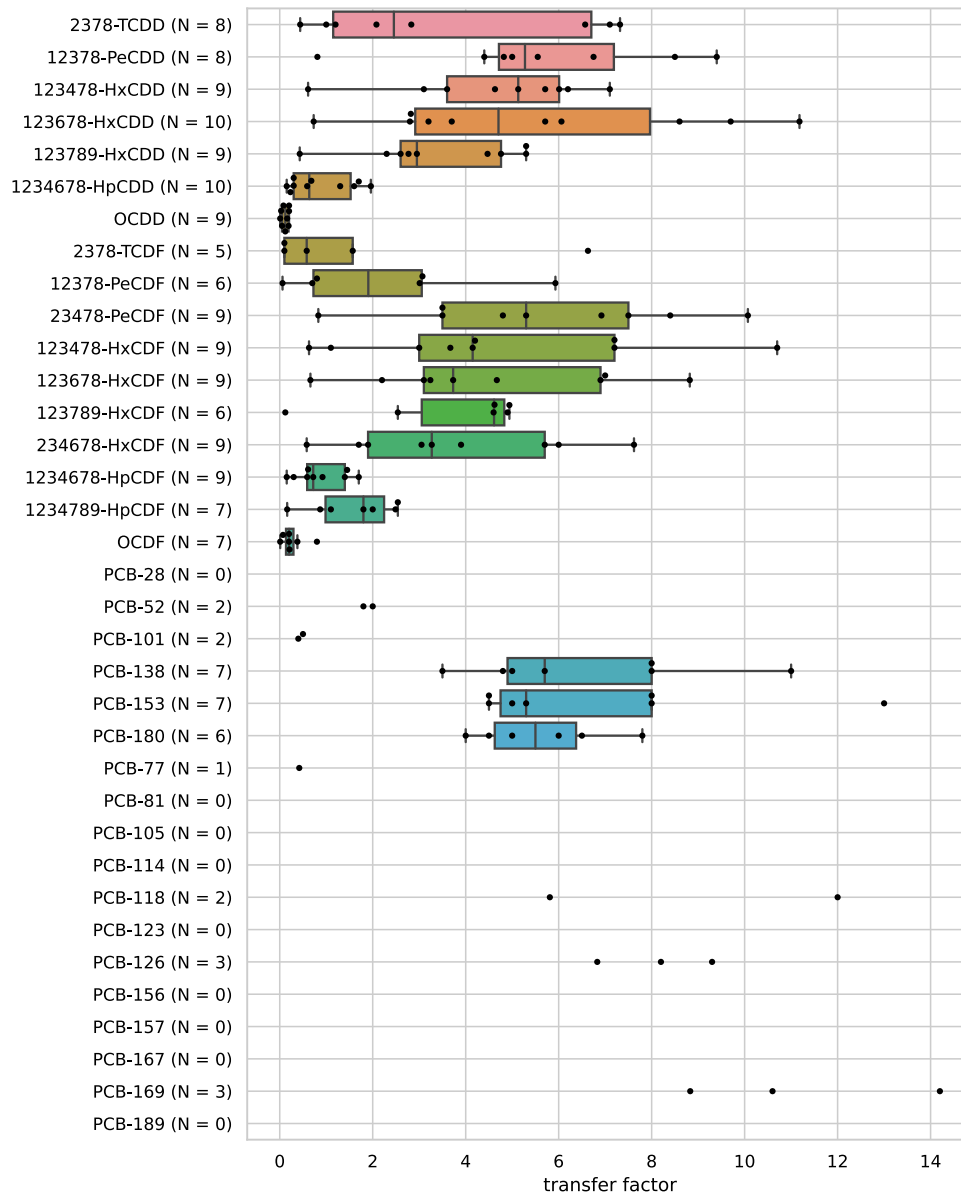
Fig. 2. Boxplots of transfer factors (TFs) in 88% dry matter basis for the feed and milk fat basis for the milk of cows. Scatter points represent available data points from selected literature (refer to Table 2). Boxes ($N > 5$) are defined as the interquartile range (IQR) between 25th percentile (Q1) and 75th percentile (Q3) of the data according to the standard method. The black line in the box represents the median. Whiskers include data within 1.5 times of IQR below Q1 and above Q3. Plot generated with Python 3.10 using the Seaborn, Matplotlib, Numpy and Pandas libraries.

concentrations in milk which are compliant with regulatory requirements after a contaminant exposure incident in a herd. At this point, an explanation is provided as to why multiple elimination half-lives are observed when the dairy cows are allowed a depuration phase after a period of exposure to lipophilic contaminants. The faster α elimination half-life dominates initially because the contaminants are readily available from the blood to be transferred into milk. This is sometimes called 'elimination phase' or 'initial phase'. Any further flow of lipophilic contaminants into milk has to come from contaminants remobilised from fat, which is a slow compartment and makes the terminal β elimination half-life slower (slower = long in time units). This is referred to as the 'distribution phase' or 'terminal phase'. The term 'distribution phase'

is not recommended for the β phase, since it coincides with the name given in the pharmacokinetics of medicinal compounds to the α phase. To better understand the physical origin of the α and β elimination half-lives, please refer to part II of this review on Toxicokinetic Predictive Models for Risk Assessment[56].

Unfortunately, most studies neglect inclusion of a depuration period, as animals were slaughtered directly after exposure to assess the distribution of contaminants into various body compartments. Even if a depuration phase was included in an experiment, derived kinetics were often limited to the later and slower β phase, as the time resolution was not sufficient to observe the initial fast elimination phase. Hence, kinetic parameters for fast α elimination phase are not available for most congeners.
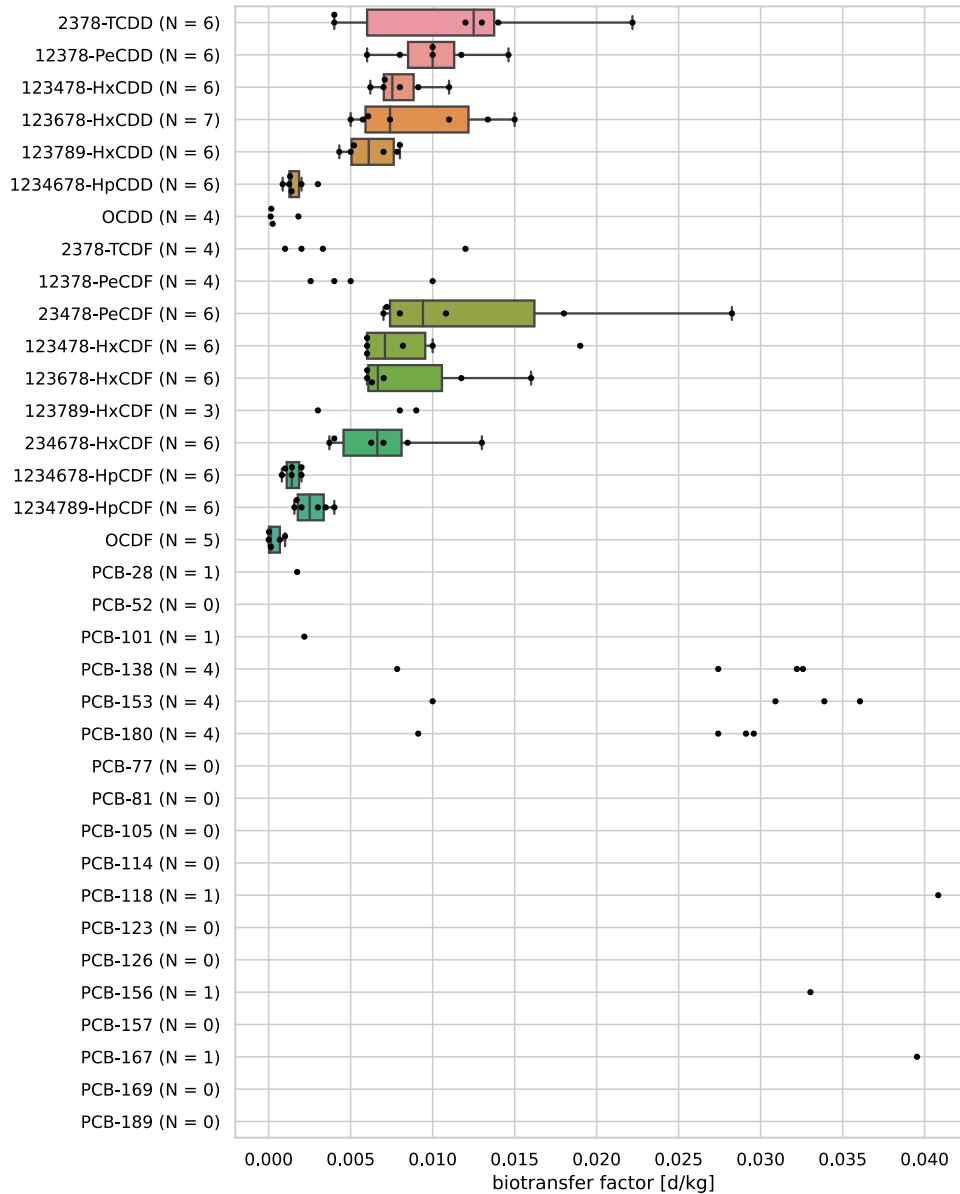
Fig. 3. Boxplots of biotransfer factors (BTFs) in whole milk basis for the milk of cows. Scatter points represent available data points from selected literature (refer to Table 2). Boxes ($N > 5$) are defined as the interquartile range (IQR) between 25th percentile (Q1) and 75th percentile (Q3) of the data according to the standard method. The black line in the box represents the median. Whiskers include data within 1.5 times of IQR below Q1 and above Q3. Plot generated with Python 3.10 using the Seaborn, Matplotlib, Numpy and Pandas libraries.

α half-lives derived from the initial fast elimination phase are plotted in Fig. 4, with the statistical data listed in Supplementary Materials Part A, Table S4. However, the information on α half-lives is sparse at best. For the majority of the PCDD/F congeners, only two studies contained values for the α elimination phase[114,135], whereas kinetics for 1,2,3,7,8-PeCDF, 1,2,3,4,7,8,9-HpCDF and several PCBs is still unknown. Furthermore, the only available data for 2,3,7,8-TCDF α half-lives, as well as an indication for PCB-101 (<4 d) in dairy animals, are derived from a study with four alpine goats[148]. Three congeners were studied in more detail, namely 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD and 2,3,4,7,8-PeCDF[61,79,91,114,116,135,148]. According to these data, half-lives range from less than 1 d for OCDF and up to 2 weeks for 1,2,3,4,6,7,8-HpCDD.

Furthermore, the data show high variation, especially for 2,3,7,8-TCDD.

β half-lives are distinctly longer than α half-lives, ranging from days to several months, and are plotted in Fig. 5 on the basis of statistical data depicted in Supplementary Materials, Table S5. Again, data for several dl-PCBs, ndl-PCB-28 and 1,2,3,7,8-PeCDF are unavailable. Furthermore, data for OCDF, PCB-169, PCB-52 and PCB-101 are available from only one feeding[135] and one field study[108], respectively. Additional data for cows were derived from feeding studies[76,82,88,91,114,135], single exposure studies[77,102], exposure during the dry phase[61,91], field studies[104,108] and incident studies[35,41] and for alpine goats[148] as listed in Table 3. Half-lives from the study by Roos et al. (1991)[61] were re-evaluated by Tuinstra et al. (1992)[116], which

Fig. 4. Boxplots of α elimination half-lives. Scatter points represent available data points from selected literature (refer to Table 3) mostly for cows, with red dots indicating data from goats. Boxes (*N* > 5) are defined as the interquartile range (IQR) between 25th percentile (Q1) and 75th percentile (Q3) of the data according to the standard method. The black line in the box represents the median. Whiskers include data within 1·5 times of IQR below Q1 and above Q3. Plot generated with Python 3.10 using the Seaborn, Matplotlib, Numpy and Pandas libraries.

were used for the present data analysis. Half-lives expressed in weeks[35] or months[100] were converted to days by multiplying the value by 7 or 30, respectively.

The heterogeneity of the experimental conditions and methodical approaches under which the data have been derived could be one reason for the variability evident in Fig. 5. Furthermore, the high variance for PCB-180 could be explained with the inclusion of β half-lives from goats, which are shorter compared with half-lives derived from cows[100,108]. Fournier *et al.* (2013) explained this with the small body fat compartment and the relatively high milk fat yield seen in goats compared with cows[148].

Aside from congener-specific data, α half-lives for sum parameters such as Aroclor 1254[70,71,78,96], ΣPCDDF/s, Σdl-PCBs and Σndl-PCBs[148], I-TEQ[61], WHO$_{1998}$-PCDD/F-TEQ and WHO$_{1998}$-dl-PCB-TEQ[82,135] as well as WHO$_{2005}$-PCDD/F-TEQ[42] are available. Furthermore, β half-lives are available for Aroclor 1254[70,71,78,119,156], ΣPCDDF/s and Σdl-PCBs[148] Σndl-PCBs[88,148], I-TEQ[35,61,102,105], WHO$_{1998}$-PCDD/F-TEQ and WHO$_{1998}$-dl-PCB-TEQ[82,135] as well as WHO$_{2005}$-PCDD/F-TEQ[41,42].

Proposing transfer parameters for the sum of congeners may be useful for practical applications, but as sum parameters (such as TEF) change, these models lose their relevance. Furthermore, congener profiles in foods of animal origin and feed can be used as forensic tools to identify contamination sources[14]. Congener-specific reporting is mandatory for risk analysis.
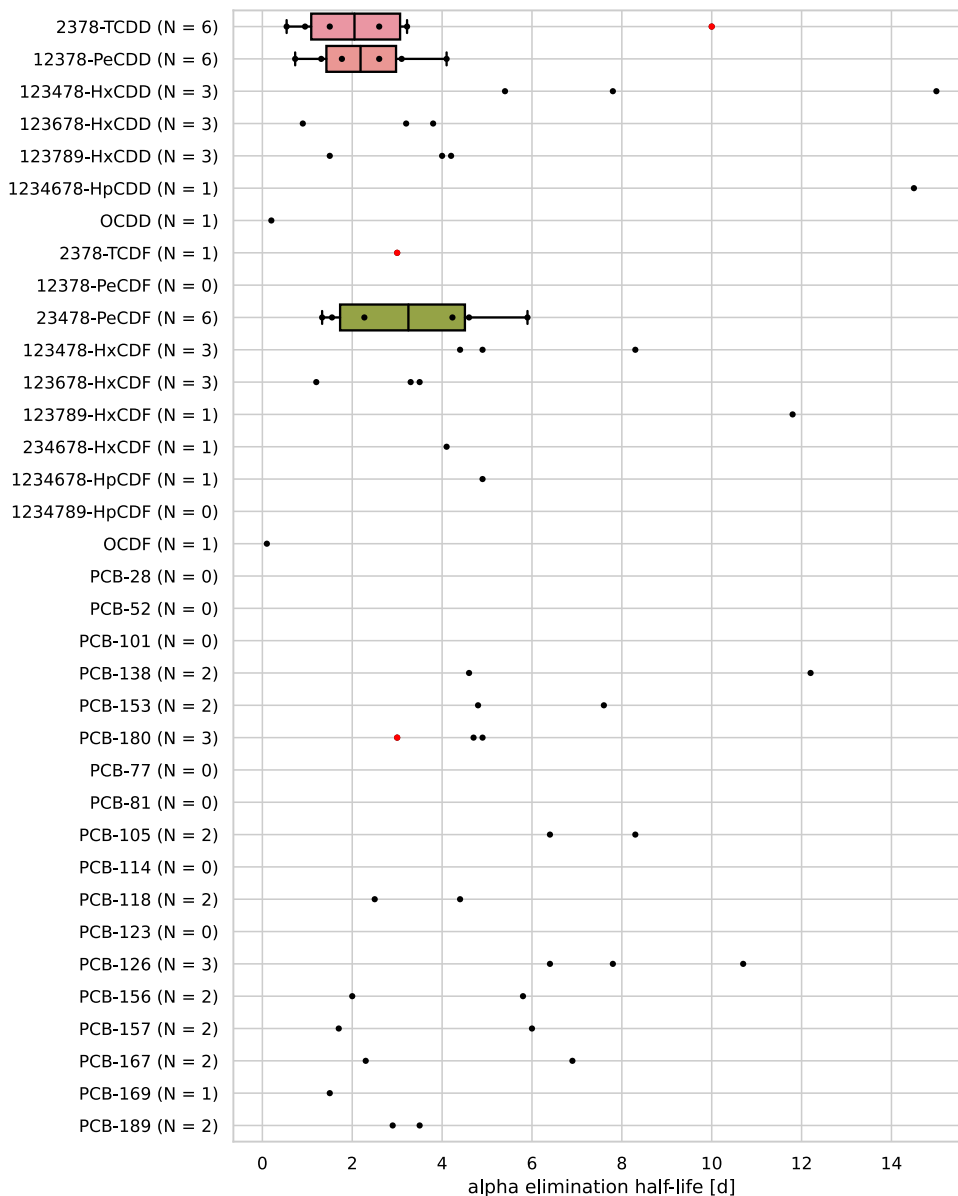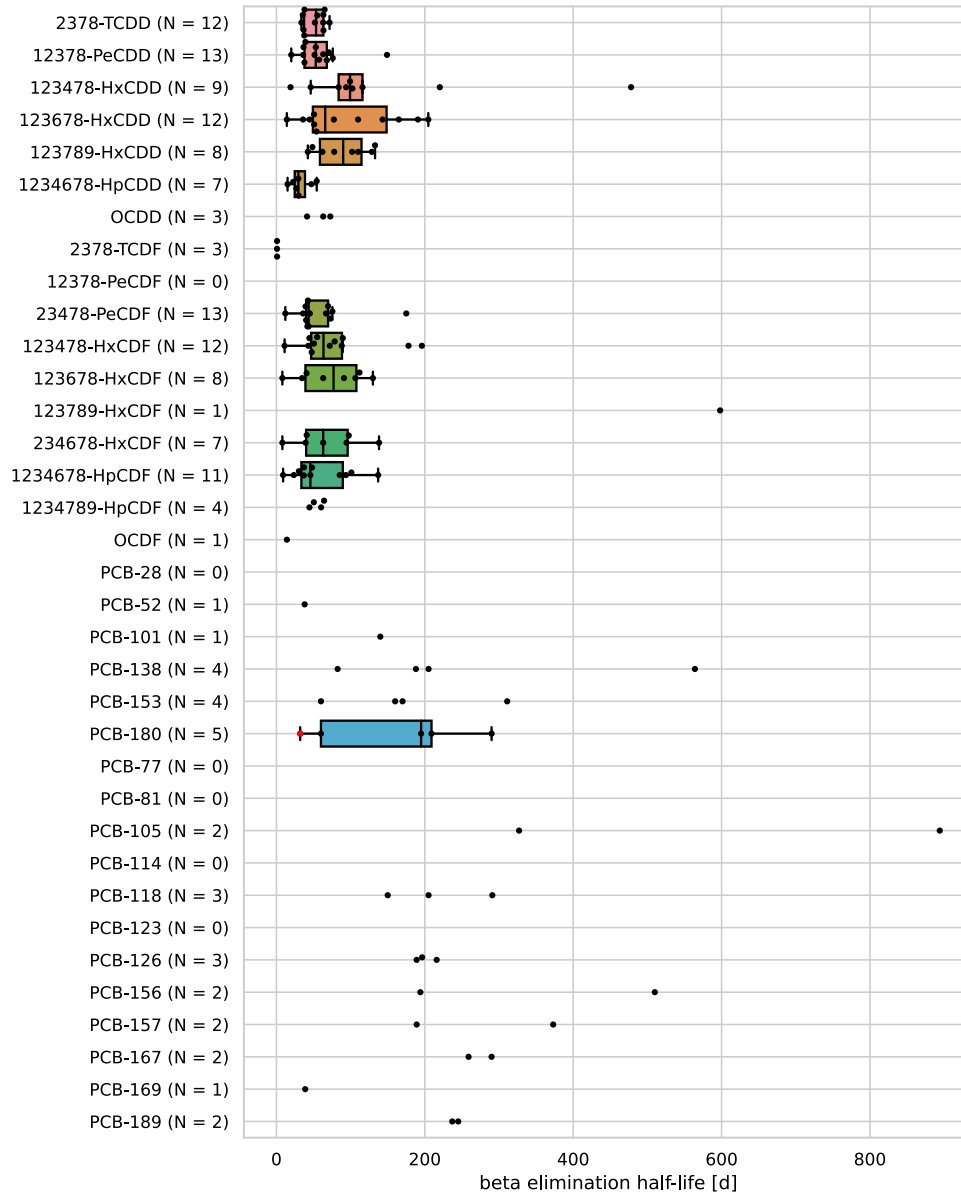
Fig. 5. Boxplots of β elimination half-lives. Scatter points represent available data points from selected literature (refer to Table 3), mostly for cows with red dots indicating data from goats. Boxes (N > 5) are defined as the interquartile range (IQR) between 25th percentile (Q1) and 75th percentile (Q3) of the data according to the standard method. The black line in the box represents the median. Whiskers include data within 1.5 times of IQR below Q1 and above Q3. Plot generated with Python 3.10 using the Seaborn, Matplotlib, Numpy and Pandas libraries.

A number of transfer parameters for this substance class can be summarised, but they are rarely all reported in a single study. As a consequence, for the parameters mentioned, not many reliable data points are available. In addition, the parameters display high variability. Possible factors influencing transfer parameters in experimental studies are discussed in depth according to the cow's metabolic state and the contaminant properties in the following chapters.

Factors influencing transfer parameters in experimental studies

Factors that enhance or restrict the transfer from feed to milk can be classified into two categories. The first category is the cow

with its individual metabolic state, health and performance parameters[141]. The second category is determined by the contaminants, their physico-chemical properties and their interaction with the animal metabolism[157].

Factors stemming from the cow's metabolic state

Especially in high-performance cows, the energy requirements cannot be completely covered by the feed intake during early lactation. The resulting metabolic state of negative energy balance (NEB) needs to be offset by mobilisation of body reserves (mainly body fat). The tides are turned approximately 80–120 d after calving into a metabolic state with positive energy balance (PEB) thanks to increased feed intake capacity, leading to

Table 4. Overview of the lactational status defined by days in milk (DIM) of cows in selected studies at beginning to end of the exposure phase to discuss the influence on transfer parameters

Reference	Early lactation (DIM)	Mid lactation (DIM)	Late lactation (DIM)
Fries *et al.* 1972[70]	Not specified (*N* = 9)	Not specified (*N* = 16)	Not specified (*N* = 6)
Fries *et al.* 1973[71]	39–99	143–203	206–266
	46–106	159–219	207–267
	48–108	161–221	211–271
Willett *et al.* 1982[78]	70–90	98–118	198–218
	82–102	119–139	239–259
		123–143	
		128–148	
		174–194	
		182–202	
Ewers *et al.* 1987*[88]	30–86	120–176	180–236
	60–116	150–206	
	60–116		
Schulz, 2005[93]	71–141	118–188	190–260

* Calculated from month p.p. multiplied by 30 d.

growing body fat reserves during later lactation. Thus, the contribution of mobilised body fat to total milk fat production is proportionally higher during the NEB in early lactation. During the later lactational stages in PEB, mainly *de novo* fat synthesis from ruminally produced short chain fatty acids and (in part) dietary fatty acids are the main source of milk fat[65,158]. Body fat mobilisation in NEB and weight gain in PEB are assumed to be of major importance when discussing the release and deposition of lipophilic contaminants in lactating ruminants[52,54,123,159]. On the one hand, during NEB lipophilic contaminants might be released from body fat depots and excreted via milk[66,99]. On the other hand, in PEB initial concentrations of contaminants in the body fat would be 'diluted' in the fat compartment, and the reservoir for storage of these compounds increases[66]. Furthermore, distribution kinetics between blood and body fat depend on the blood/fat surface area, which increases with growth of body fat. A greater blood/fat surface area supposedly increases the transfer coefficient for blood/fat diffusion of lipophilic contaminants and affects their elimination through milk[159]. As a consequence, differentiation of lactational stages into 'early', 'mid' and 'late' should be made to understand possible differences in transfer rate and α or β elimination half-lives (Table 4).

However, the influence of the metabolic state on the transfer of PCDD/Fs and PCBs into milk is still ambiguous in view of several field observations and feeding studies. For example, no increase of PCDD/Fs in milk fat was observed during nutritionally induced body fat mobilisation[94]. Three studies[66,78,88] analysed the influence of NEB and PEB on the transfer of PCBs to milk during lactation. Thomas *et al.* (1999) conducted a long-term mass balance study in which the cows transitioned metabolic phases and described higher TRs for several PCBs during NEB than in PEB phase[66]. Similarly, Willet and Liu (1982) observed that excretion of PCBs was elevated for cows early in lactation compared with cows late in lactation[78]. In contrast, Ewers (1987) described divergent effects of the lactational stage on the transfer of ndl-PCBs at two different dosage levels[88]. At the lower dosage, the TRs of ndl-PCBs were lower in early lactation, while no effect from the lactation period was evident with a 67% higher dose of the same ndl-PCB mixture on TRs, TFs and

elimination half-lives. On the basis of the current data, no conclusive statement can be made on the influence of the lactational stage.

Regarding milk elimination half-lives, Brambilla *et al.* (2008) observed very short β half-lives compared with other studies in a herd of dairy cows after PCDD/F contamination. The authors attributed these findings to the physiological status of the herd, with 25% of the cows likely being in a negative energetic balance[41]. Fries *et al.* (1972) observed a tendency towards lower mean first-order rate constants for Aroclor 1254 depuration (half-lives were greater) for cows in early lactation compared with mid- and late lactation (Table 4)[70]. However, no statistics were analysed to underline this statement. Importantly, a follow-up feeding study with nine cows in different stages of lactation saw no consistent relation between the first-order rate constants and the rate of body weight change[71].

Depuration kinetics of PCBs were further studied under the influence of a thyroprotein supplement, which induced body fat mobilisation and increased milk and milk fat production. During the thyroprotein treatment, elimination of PCBs in milk fat increased compared with a control group[78]. Furthermore, Farries (1990) studied the excretion of ndl-PCBs in fifty dairy cows fed according to their energetic needs. During the depuration phase, half of the cows were purposely undersupplied by 30%, resulting in weight loss and a decrease in milk yield. The resulting fat mobilisation also caused a slight initial increase of PCB content in milk fat, whereas the PCB milk fat content in the energetically balanced cows further decreased[59].

During the dry period before lactation, the most important elimination pathway for the excretion of PCDD/Fs and PCBs through milk is not available, leading to increased bioaccumulation in body fat of the pregnant cow and the foetus. Several feeding studies described the exposure of animals during the dry period and observed transfer and elimination kinetics in milk postpartum with different results. Several studies observed a rapid decline of PCBs and PCDD/Fs in colostrum[88,93,94,100,116], whereas Hirako (2008) described a decline for most PCDD/Fs congeners while the dl-PCB content in colostrum and milk lipids was nearly constant[127]. Klein *et al.* (1992) stated that high milk yields promoted fast depuration postpartum[100], and Tuinstra

et al. (1992) postulated that the depuration kinetics for PCDD/Fs postpartum could be different later in lactation[116]. Furthermore, Ewers *et al.* (1987) estimated TRs on the basis of the accumulative input and output, and stated that these TRs were higher in early lactational state compared with TRs derived from cows later in lactation[88]. Differences in body fat dynamics, PCDD/F and dl-/ndl-PCB absorption or metabolic clearance rates may also be attributed to parity[114].

Body weight and body fat content

Aside from dynamic changes in body fat due to metabolism, the size of the fat compartments is an important factor for distribution and storage of lipophilic substances like PCDD/Fs and PCBs. However, quantification of fat compartments in a living animal is challenging. Hence, proxies, such as body weight or verbal description of the body fat content, are used to explain the influence of fat compartment sizes on transfer kinetics.

Fries *et al.* (1973) concluded that there was no connection between body weight of the cows and elimination half-lives in milk[71]. In a follow-up study in 1999, the same authors observed no connection between transfer rates and body weight[72], whereas by contrast, McLachlan and Richter (1998) suggested that TR could be influenced by body weight, albeit not strongly[113].

Ewers *et al.*[88–90,131] noted that TR increased with decreasing body fat percentage, though milk yields and dosage levels also need to be considered. On the basis of data from the feeding study published by Ewers *et al.*[88,89,131], Heeschen *et al.* (1993) stated that the biological half-lives of PCBs in cows with an elevated body fat percentage are twice as high compared with animals with an estimated low body fat percentage, regardless of milk fat yield[132].

In another study, shorter half-lives for a cow with low body fat compared with three other cows were calculated. The authors postulated that with a lower body fat weight the volume for distribution of lipophilic substances would also be small, and thus the transfer from body fat to milk would be elevated[61,116]. A similar observation regarding the decline of PCB concentrations in milk of two cows with different body weights was described by Klein (1991)[99].

Milk and milk fat production

The lipid content of milk depends on the lactation stage, individual animal, breed and feed composition. Furthermore, the daily milk fat production is related to the daily milk yield and the metabolic state of the cow. Both of these performance parameters have been steadily increased through breeding measures for dairy cows[160], a trend that also reflects in data of the cited transfer studies (Table 5).

Owing to the lipophilic nature of PCDD/Fs and PCBs, these compounds have a high affinity to milk lipids. It is therefore reasonable to assume that the daily milk fat yield has an effect on the transfer parameters. McLachlan *et al.* (1998) stated that the interaction of PCDD/F TRs and lactation rate, among other factors, is not very pronounced[113]. Other studies mentioned a positive correlation between milk yield[72,135] or milk fat yield[73] and the TRs of PCDD/Fs into milk. TFs of PCDDF/s were found to

be less dependent on milk production, but could be related to milk fat content[72].

In a feeding study, total recovery of ndl-PCBs (PCB-138, PCB-153 and PCB-180) in milk was higher in a cow with higher milk yield but also lower body fat percentage compared with another cow with less milk yield and higher body fat percentage[87]. In a follow-up experiment with three cows, TRs increased with higher milk yields and lower body fat percentages[88,89,131,132]. These observations coincide with a recent feeding study with primiparous (lower milk fat yield, lower body weight) and multiparous (higher milk fat yield, higher body weight) cows, suggesting that lower milk fat yields could be one reason for lower PCDD/F and dl-/ndl-PCB TRs[114].

The influence of milk fat and milk yield on the depuration phase was discussed in several studies. Klein *et al.* (1992) stated that differences in milk fat production at comparable milk yields did not clearly correlate with PCB excretion rates[100]. Heeschen *et al.* (1993) assumed that the mean milk fat production had no effect[132], and Rossi *et al.* (2010) concluded that averaged daily milk yields per cow did not affect the rate of PCB excretion[123]. Furthermore, Fries *et al.* (1973) found no significant correlation between milk fat production per cow and PCB excretion rates[71].

However, Klein *et al.* (1992) also stated that elimination half-lives from cows, with comparable body weight and PCB milk fat content before depuration, were shorter with higher milk yields[100]. Recently, Driesen *et al.* (2022) derived overall shorter PCB elimination half-lives for multiparous cows with higher milk fat yields compared with primiparous cows. However, a dependency between elimination half-lives calculated for PCDD/Fs and milk fat yield was less conclusive, with half-lives for PCDD/F TEQs being even shorter for primiparous cows[114].

Overall, variation of milk fat production within singular studies could be too small to observe significant effects on transfer parameters. Therefore, the influence of this factor cannot be assessed conclusively on the basis of the current data situation.

A final potentially important factor is the milk fat origin in terms of its proportion from *de novo* synthesised milk fat to remobilised body fat, as discussed above in the section on metabolic state.

Animal health

Little is known on whether animal health status has an impact on the transfer of PCDD/Fs and PCBs into milk. Absorption of PCBs in the gastrointestinal tract might be restricted by diarrhoea as the passage of feed is accelerated. Hence, the transfer into milk and tissue fat is reduced compared with healthy cows[74]. Mastitis, on the other hand, might promote the transfer of PCDD/Fs into the milk, as the mammary gland blood–milk barrier becomes more permeable[72]. Field studies and incident investigations on PCDD/F and PCB contamination rarely mention the animal health status. Thus, a possible influence on the results of the studies included in this review can neither be excluded nor confirmed.

In turn, PCDD/F and dl-PCB exposure may have effects on animal health, such as oxidative damage combined with reduced levels of antioxidants in the blood[161,162] and chromosome fragility[163]. Exposure to elevated levels of TCDD was even

Table 5. Milk and milk fat production of selected studies in chronological order

Reference	Breed	N	Milk yield (kg/d)	Milk fat yield (kg/d)	Milk fat (%)
Fries *et al.*, 1973[71]	Holstein	1	17.7	0.72	4.1
	Holstein	1	15.3	0.62	4.1
	Holstein	1	11.9	0.51	4.3
	Holstein	1	18.3	0.72	3.9
	Holstein	1	14.5	0.61	4.2
	Holstein	1	20.8	0.78	3.8
	Holstein	1	22.7	0.88	3.9
	Holstein	1	22.9	0.79	3.5
	Holstein	1	21.9	0.75	3.4
Heeschen *et al.*, 1986[87]	German Holstein	1	18.8*		
	German Holstein	1	24.2*		
	German Holstein	1	21.5*		
Ewers, 1987[88]	German Holstein	1	20	0.94	
Ewers *et al.*, 1987[89,131]	German Holstein	1	29	1.39	
Heeschen *et al.*, 1993[132]	German Holstein	1	22	1.04	
	German Holstein	1	23	0.73	
	German Holstein	1	23	0.87	
	German Holstein	1	21	0.78	
Ewers *et al.*, 1989[90]	German Holstein	1	8.1*		
	German Holstein	1	17.2*		
	German Holstein	1	18.6*		
Klein, 1991[99]	German Black Pied	1	18.7*		
Klein *et al.*, 1992[100]	German Black Pied	1	25.5*		
	German Black Pied	1	22.4*		4.43
	German Black Pied	1	21.4*		3.17
	German Black Pied	1	20.8*		3.69
McLachlan *et al.*, 1998[113]	Simmental	1	26.8		
	Simmental	1	16.4		
	Simmental	1	27.7		
	Simmental	1	17.9		
Fries *et al.*, 1999[72]	Holstein	1	31·1–27.9	1.27–1.10	
	Holstein	1	37.2–34.1	1.48–1.33	
	Holstein	1	12.1–9.1	0.58–0.47	
	Holstein	1	25.2–22.9	1.00–0.87	
Fries *et al.*, 2002[73]	Holstein	4		0.85	
	Holstein	2		1.66	
Huwe *et al.*, 2005[135]	Holstein	1	19.5		3.01
	Holstein	1	25.2		3.08
Rossi *et al.*, 2010[123]	Unknown	1	26.0		
	Unknown	1	22.5		
	Unknown	1	23.2		
	Unknown	1	24.5		
	Unknown	1	28.9		
	Unknown	1	29.3		
Driesen *et al.*, 2022[114]	Simmental	2	9.2	0.32	3.47
	Simmental	2	13.2	0.56	4.28
	Simmental	4	10.1	0.35	3.59
	Simmental	4	13.5	0.56	4.13

* Calculated from L/d by multiplying with a density of 1.04 kg/l and rounded to one decimal place.

suspected to be the cause of abortions and stillbirths in cattle[164]. However, the European Food Safety Authority (EFSA) concluded that all the above-mentioned studies are not fit for risk assessment owing to missing data or exposure to other potential hazardous substances[16].

No adverse effects on the conversion of feed to milk or body weight were observed in dairy cattle exposed to high amounts of 1 g/d (1.7 mg/kg body weight/d[121]) Aroclor 1254[81] over several days. Furthermore, during *in vitro* fermentation experiments on micro-organism activity from the rumen of Holstein steers, no effect in terms of dry matter disappearance was observed in presence of different PCB concentrations. The toxic effects of ndl-PCBs on laboratory animals are generally difficult to identify,

since they rarely appear in a pure form. Even less information is available on specific effects of ndl-PCBs on the health status of dairy cows. It can be expected that very high doses of pure ndl-PCB 180 might have neurotoxic, endocrine and behavioural effects[165], but such doses are not expected in practice for farm animals.

Factors stemming from the contaminants

Dosage. Owing to substantial progress in analytical techniques, the limits of quantification for PCDD/Fs and PCBs in milk fat have steadily decreased during the past decades. Therefore, smaller daily doses could be applied during feeding studies

while ensuring the quality of the derived transfer kinetics. This development is also in accordance with regulatory efforts that helped to reduce the overall exposure of ruminants to PCDD/Fs and PCBs through feed in the past decades. Furthermore, several feeding studies in the 1970s and 1980s applied varying daily concentrations to evaluate the correlation between dosage level and transfer into milk and or milk fat.

Platonow *et al.* (1971) noticed an approximately ten-fold increase of Aroclor 1254 in whole milk, and a more than ten-fold increase in cream, with a ten-fold increase of the daily dosage[95]. However, Arnott *et al.* (1977) stated, on the basis of single- and multiple-dosage studies with Aroclor 1254, that proportionally less PCBs are excreted with the milk at higher doses (higher dose, lower TR)[98]. The tentative mechanism proposed was a dose-dependent decrease in absorption.

Willet *et al.* (1990) re-evaluated the quantification of Aroclor 1254 in milk fat from earlier studies and found a significant linear correlation between dosage and PCB concentrations in milk fat[121]. Contrastingly, an increase of TRs for the three indicator PCBs 138, 153 and 180 was observed at higher exposure and decreasing body fat percentage[88,89].

For PCDD/Fs, only one study stated an increase in 2,3,7,8-TCDD residues in milk and cream in proportion to the daily dose[77]. Dose-dependent absorption[166] or self-induced metabolism of the contaminants[167] are two possible mechanisms that could be responsible for the lack of linearity between the oral dose rate and the milk fat correlation response. However, these mechanisms have been proposed for other species; therefore, the conclusions regarding the influence of the dosage are still not clear for dairy cattle.

Contaminant source-dependent bioavailability

Ruminants may be exposed to PCDD/Fs and PCBs via various sources, such as roughage, concentrates and mineral supplements, but also wall paints and wood preservatives, soil, sewage sludge and fly ash. The bioavailability of the contaminants from different sources (matrices, Table 6), that is, primarily the absorption of PCDD/Fs and PCBs by the ruminants, needs to be considered when discussing transfer parameters. Furthermore, PCBs have also been administered intravenously[120] as well as intramuscularly[125] to sheep.

On the basis of two successive mass balance studies, McLachlan *et al.* (1998) concluded that digestive tract absorption of PCDD/Fs from sewage sludge, as the contamination source for grass silage, was comparable to grass silage contaminated by atmospheric deposition[113]. The bioavailability of PCDD/Fs in fly ash collected from a filter of a municipal solid waste incinerator and administered intra-ruminally was lower than the value estimated for grass from a pasture near a large municipal solid waste incinerator[62]. TFs of PCDD/Fs derived from a feeding study with pentachlorophenol-treated wood[72] compared with a study with contaminated magnesium mineral supplement suggested a reduced bioavailability of PCDD/Fs from pentachlorophenol-treated wood[82].

Fürst *et al.* (1993) stated that soil intake of grazing cows is either less than assumed or that the bioavailability of PCDD/Fs from soil is lower than expected[122]. A lower bioavailability of

Table 6. Transfer studies grouped according to the contamination source

Reference	Exposure source matrix
(67,68,72,84,109–111,123)	Various feed stuffs
(61,63,65,66,70,78,83,85,113–115,119,148)	Silage (i.e. grass, maize)
(59,63,99,112,144,145)	Hay
(79,80)	Grain
(57,61,71)	Concentrate
(35,105)	Citrus pulp pellets
(43,83)	Sugarbeet
(142)	Kliba pellets
(42)	Potato peels
(41,82,135)	Mineral supplement
(149)	Complementary feed
(63,104,106)	Grass
(114,117,146,147)	Soil
(62,69,93,94,108,118,122)	Grass and soil
(74)	Paper
(72,73)	Wood
(62,103)	Fly ash
(86,95,98,102,124,125,147)	plant oil (olive, sunflower, maize)
(77)	Silica gel
(60,75,76,81,87,88,90–92,97,120)	Gelatine capsule
(87,151)	Unknown

several PCDD/Fs and PCBs from soil was also hypothesised by Driesen *et al.* (2022), who calculated tendentially higher TRs for a control group fed grass-silage compared with another group fed grass-silage mixed with contaminated soil[114]. However, according to several studies with goats and cows, bioavailability of PCBs from soil is comparable to maize silage[148], hay[146] or grain[80]. Compared with a spiked oil matrix, the bioavailability of PCBs from a sandy soil contaminated by a fire is slightly reduced[147].

The absorption of PCDD/Fs from contaminated lime, when used as a neutraliser for acidic citrus pulp, is comparable to that of grass. During this process, the lime is completely dissolved and the PCDD/Fs are absorbed in the citrus pulp[35]. Slob *et al.* (1995) hypothesised increased lipid content and smaller particle sizes as factors that could increase bioavailability[62]. An overview of various TFs according to different matrices as carriers for the contamination is given by Huwe *et al.* (2005)[135], in which the substantially lower TFs for fly ash and grass contaminated with municipal solid waste[62] are attributed to particulate binding[135]. Furthermore, bioavailability of PCDD/Fs and PCBs also depends on the physico-chemical properties of the congeners, such as degree of chlorination.

Degree of chlorination and partition coefficients

The octanol-water partition coefficient K_{ow}, as well as its logarithm log (K_{ow}), are widely used measures of the lipophilicity of a compound. K_{ow} correlates with the *in vivo* thermodynamic equilibrium partition (or preference) of the congeners among water-rich and fat-rich tissues. In turn, the number of chlorine atoms in PCDD/F and PCB congeners correlates with K_{ow}. With more chlorine atoms in a congener, its K_{ow} increases, and its solubility preference for the aqueous phase decreases[168]. All PCDD/Fs and PCBs have a K_{ow} larger than 1, which implies that these substances are lipophilic and hydrophobic, hence their

distribution into body and milk fat. K_{ow} values are used to predict toxicokinetic model parameters, since they correlate with the preference of contaminants for different compartments, such as blood, tissues and udder fat in the cow. The TRs[64,86,109,113,144,169], BTFs[72] and bioavailability[102] of 2,3,7,8-substituted PCDD/Fs, with the exception of 2,3,7,8-TCDF and 1,2,3,7,8-PCDF, decrease with the number of chlorine substituents. This behaviour can be attributed to a decrease in absorption over the gastrointestinal wall[108,112], due to the increased hydrophobicity of highly chlorinated PCDD/Fs[63].

Furthermore, lower chlorinated PCDD/Fs migrate principally into the lipoprotein fraction of blood, while higher chlorinated PCDD/Fs bind more readily to other blood plasma proteins with a prolonged dwell time in systemic circulation[127,170]. In addition, the extent of deposition of PCDD/Fs into subcutaneous fat was found to be inversely correlated to the degree of chlorination. This could explain the faster elimination rates of hepta-chlorinated PCDD/Fs compared with lower-chlorinated congeners[102]. A faster distribution of lower-chlorinated PCDD/Fs from liver to fat tissues was also observed by Richter and McLachlan (2001), who found that higher-chlorinated PCDD/Fs were accumulated in the liver[171], likely owing to the low affinity of these compounds to lipoproteins[127,169]. Other studies found no correlations between elimination half-lives and the number of chlorine substituents[116,135].

Fluxes of PCBs in faeces of cows showed that absorption in the gastrointestinal tract also decreased with increasing degree of chlorination[111]. Furthermore, the residence times of PCBs in the cow, calculated as body burden divided by amount absorbed, increased with the degree of chlorination[65]. TRs derived in studies with lactating alpine goats also showed no clear correlation[146] or indications for an inverse correlation with degree of chlorination[144]. However, aside from the degree of chlorination and K_{ow}, the substitution pattern, and thus metabolic stability, also needs to be considered when discussing effects on transfer parameters.

Metabolism of PCDD/Fs and PCBs

PCDD/Fs and PCBs are known to be persistent in the environment, with half-lives of up to several decades[12]. However, some congeners are more readily enzymatically metabolised by the cow, with the velocity and extent being largely dependent on the chlorination pattern. One metabolic pathway is the typical phase-1 metabolism, that is, hydroxylation of PCBs in the animal and subsequent excretion via urine and, to a lesser extent, via milk[75,120].

However, metabolism of PCBs is congener specific. One hypothesis is that PCBs with a 4,4′-substitution pattern and, to a lesser degree, with a 2,3,5-substitution pattern, are less likely to be metabolised[111]. Another hypothesis is that PCBs with adjacent meta- and para-hydrogen atoms are more chemically stable, and PCBs with adjacent ortho- and meta-hydrogen atoms are only partially metabolised[65]. However, both hypotheses have their shortcomings, as there are PCBs that do not behave as predicted by these rules in terms of substitution patterns[65].

PCDD/F congeners with a 2,3,7,8-chlorine substitution pattern are largely metabolically stable and are transferred into the milk in unchanged form, while other congeners can be metabolised in the animal[64,76,109]. Additionally, 2,3,7,8-substituted furan congeners without chlorine at 4 and 6 position[72,73], such as 2,3,7,8-TCDF[102] and 1,2,3,7,8-PeCDF[113], are susceptible to metabolism. *In vitro* fermentation experiments showed no significant metabolic degradation of PCBs[172] or PCDD/Fs[73] by rumen microorganisms.

The transfer parameters for dioxins and PCBs in experimental studies can be influenced by several factors, some attributable to the cow physiology and others related to the chemical contaminant. There are some contradictions in the literature regarding the assessment of the influence of the factors responsible for the variability in transfer parameters, often aggravated by incomplete information. Comparability is not trivial, since there are many different possible study designs, due to many variables, such as animal species and breed, milk yield, type of congener administered and duration of supplementation. On the basis of existing gaps in the data and the multitude of different studies, the literature data are not always applicable and comparable to produce predictive models. However, several toxicokinetic predictive models have been proposed and successfully parametrised in the literature, and shown to agree well at least with the specific experimental data they are based on.

Conclusions

The present review provides a comprehensive overview of the transfer of PCDD/Fs and PCBs from feed into the milk of dairy cows, and reveals several key aspects that may influence their transfer kinetics. We have identified data gaps for dairy cows regarding congener-specific BTFs, especially for PCBs, and many congener-specific elimination half-lives. Even when transfer parameters are available, there is a high degree of variability between studies, sometimes even among studies with similar experimental setups. Nevertheless, our compilation and graphical depiction of transfer parameters testify to the strong differences in kinetics for the various PCDD/F and PCB congeners. Thus, there is a necessity to separately quantify the transfer of as many congeners as possible to perform risk assessment and risk management.

It seems likely that a considerable amount of variability in transfer parameters (i.e. TR, TF, BTF and half-lives) for the PCDD/F and PCB congeners summarised here is due to the considerable heterogeneity in study design and data quality. However, a classification or weighting of influence factors is not possible, as most studies were not explicitly designed to evaluate the influence of, for example, lactational stage, breed, source or route of exposure on the transfer kinetics. The literature contains valuable indications on the dependency of transfer parameters on the aforementioned factors, but conclusions on such dependencies are sometimes based on a low sample size, so that the bias of individual animals may be confused for systematic variation. Future studies should try to address the variability by using an appropriate number of animals with clearly defined physiological conditions (e.g. breed, milk and milk fat yield, lactational stage, NEB or PEB phase, body weight/body fat weight and animal health status). Furthermore, the influence

of metabolic status on the transfer of PCDD/Fs and PCBs into milk is of special interest and yet difficult to pinpoint. Milk yield and body fat percentage are intertwined with the NEB and PEB phases of lactation but are also important factors on their own. High variability between individuals further complicates analyses. To study the effect of the metabolic status on the transfer of PCDD/Fs and PCBs, it is advisable to expose a large enough group of animals postpartum during a NEB phase and the same group again in high lactation during the PEB phase, giving enough time for depuration between both exposure phases.

Over the past decades, milk yield has increased from less than 30 kg/d to over 40 kg/d during high lactation[140]. The question arises of how existing data and models represent transfer under the ranges of the current milk yields. At the moment, existing data do not allow for a conclusive answer to this question, as experimental data for modern highly productive cows are scarce. Advanced breeding efforts will lead to further increases in milk yield, but also impact other areas of dairy cow genetics and metabolism. At the same time, ethical requirements will demand a reduction in animal numbers in forthcoming feeding trials. Thus, the question arises in how far (i) data from previous studies can be utilised for predicting the transfer of contaminants in future breeds and (ii) valid conclusions can be drawn from smaller animal studies. Both issues are closely related to the advancement of prediction tools and toxicokinetic modelling approaches. These topics are the subject of the part II of the present review article[56].

In this review, we have highlighted where the gaps in experimental data lie and hope to aid future researchers to design the experiments of the future (and the models they engender) to support PCDD/F and PCB risk assessment and risk management of milk products.

Conflict of interest

None.

Authorship

Torsten Krause: literature search, data compilation and analysis, writing (original draft), figures

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S0954422422000178.

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