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POLYFLUORINATED DIBENZODIOXINS AND DIBENZOFURANS - SYNTHESIS, ANALYSIS, FORMATION AND TOXICOLOGY

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ABSTRACT

The 75 congeners of the polyfluorinated dibenzodioxins (PFDDs) and about half of the 135 polyfluorinated dibenzofurans (PFDFs) have been synthesized by pyrolysis of fluorophenols and fluorobenzenes. The individual congeners were characterized by GC/MS. 2,3,7,8-TFDD was also characterized by ^{1}H-, ^{13}C- and ^{19}F-NMR spectroscopy. The retention behavior of PFDDs and PFDFs during gaschromatographic separation is entirely different from that of PCDDs/PCDFs or PBDDs/PBDFs. The PFDDs/PFDFs elute earlier than the PCDDs/PCDFs and the order of the elution is not governed by the degree of substituion, O_8FDD eluting e.g. much earlier than the M_1FDDs.

A preliminary toxicological evaluation of 2,3,7,8-TFDD was carried out. The elimination of 2,3,7,8-TFDD from mice after a single i.p. injection is biphasic with a very rapid elimination half-live of 5 minutes and a slower phase of 165 minutes. This means a dramatically reduced half-live compared to 2,3,7,8-TCDD with 8.5 d. In liver the TFDD level reaches a maximum 30 minutes after injection and also declined in a biphasic manner. In rat hepatocytes a primary culture induction of CYP4501A1-catalyzed EROD activity could be demonstrated, indicating that 2,3,7,8-TFDD activates the dioxin receptor. In rat hepatocyte cultures similar EC_{50} values were found for 2,3,7,8-TCDD and 2,3,7,8-TFDD.

So far no *de novo* synthesis of PFDD/PFDF could be detected under conditions were PCDDs/PCDFs are formed Also, formation of PFDDs/PFDFs could not be detected during thermal treatment of fluorotrichloromethane or Teflon.

INTRODUCTION

In the last years the question has been raised repeatedly, whether polyfluorinated dibenzodioxins and polyfluorinated dibenzofurans are formed during chemical and/or thermal processes, as it has been shown for chlorinated, brominated and mixed chlorinated-brominated dibenzodioxins and dibenzofurans.

In order to analyse products, emissions, and environmental samples for the occurrence of polyfluorinated dibenzodioxins and dibenzofurans, it is necessary to know their analytical properties. For this purpose we synthesized all 75 PFDDs and approximately half of the 135 PFDFs, developed a clean-up procedure, and determined their chromatographic properties.

The *de novo* synthesis of PFDD/PFDF was studied and some processes were tested for the occurence of PFDD/PFDF.

A preliminary toxicological evaluation of 2,3,7,8-tetrafluorodibenzodioxin was carried out.

MATERIALS AND METHODS

Synthesis of PFDD:

The different congeners of the PFDDs were synthesized by pyrolysis of fluorophenols or flourophenates, analogous to the PCDDs [1, 2]. Another possibility of synthesis is described elsewhere [3].
1 - 100 mg of the fluorophenol and a corresponding stochiometric amount of KOH or CaH_2 were heated in a closed quartz ampule (10 cm x 2 cm i.d.) for 1 to 3 h at 280 °C. After cooling to room temperature the ampule was opened carefully. The reaction product was dissolved in 10 ml toluene by treatment in an ultrasonic bath for 15 minutes. The toluene solution was extracted 3 times with a 1 M KOH-solution. The organic layer was dried with Na_2SO_4 and the solvent was reduced to approximately 1 ml. The solution was placed on a column filled with 2.5 g of Alumina B Super I for Dioxin Analysis (ICN Biomedicals, Wesel, FRG). This "mini-alumina column" was eluted first with 20 ml of heptane/dichloromethane (98:2) followed by 20 ml of heptane/dichloromethane (1:1). The latter fraction contained the PFDDs. The solvent was removed with a rotary evaporator under controlled pressure. Due to the relatively high vapour pressure of the PFDDs complete removal of solvent has to be avoided. The PFDDs were transferred to a 3 ml vial with dichloromethane as solvent. The solvent was removed under gentle stream of nitrogen, avoiding complete dryness.

Synthesis of PFDFs:

PFDFs were synthesized by pyrolysis of fluorophenols and fluorobenzenes. In addition pyrolysis of fluorophenols without fluorine substitution in ortho position to the hydroxyl group was carried out.
1-20 mg of fluorophenol and approximately a three fold amount of fluorobenzene or only fluorophenols without substitution in 2 position were heated in a closed quartz ampule (10 cm x 2 cm i.d.) for 1-5 h at 280-380 °C. As catalysts for the condensation CuO/Zn/Ca were used.
The clean up was carried out analogous to the PFDDs.

NMR-characterization of 2,3,7,8 TFDD:

The ^{1}H-NMR- and the ^{13}C-NMR-spectra were obtained on a Bruker AC 250, the ^{19}F-NMR-spectrum on a Bruker AMX 600.

Toxicokinetic study:

Male NMRI mice (20-23 g body weight) were treated with a single i.p. dose of 100 µg 2,3,7,8 TFDD/kg, dissolved in corn oil. At various time points, animals were anesthetized with ether and blood samples were taken. Then the mice were sacrificed, and livers were removed for TFDD analysis.

Toxicological evaluation:

Hepatocytes from male Wistar rats were plated at a density of 100 000 cells per cm^2 on collagen-coated petri dishes in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10 % fetal calf serum, 10 % calf serum, and 10^{-7} M dexamethasone. After 24 h in culture, various concentrations of 2,3,7,8 TFDD, freshly dissolved in DMSO, were added, cells were harvested 48 h later, and EROD activity was determined in cell homogenates as previously described for PCDDs [4]. For comparison, hepatocytes were incubated with 2,3,7,8 TCDD. Log probit functions were fitted to the data by use of SAS probit procedure which also allows estimates for EC_{50} values.

GC/MS analysis:

The analysis for PFDD/PFDF was carried out with a HP 5890 gaschromatograph coupled directly to a HP 5970 mass selective detector. A CPSil-88 fused silica column (50 m, 0.25 mm i.d., 0.2 µm film thickness, CHROMPACK, Frankfurt) was used. Sample aliquots of 1-3 µl were injected splitless (injector temperature

250°C) and the column temperature was programmed as follows: 90 °C; 2.7 °C/min to 150 °C, 4 min isothermal; 8°C/min to 170 °C, 3 min isothermal; 20 °C/min to 245 °C. Carrier gas was helium at a head pressure of 150 kPa. For characterization of the PFDDs/PFDFs full scan mass spectra were obtained. For quantitative analyses the mass spectrometer was run in the SIM mode. For PFDD mass fragmentograms at M^+, $(M-47)^+$ and $(M-56)^+$, for PFDF M^+, $(M-29)^+$ and $(M-47)^+$ were registered. Quantitation was carried out either by external or internal standardization with octafluordibenzodioxin and 2,3,7,8-TCDD, respectively.

Study of *de novo* synthesis of PFDDs/PFDFs on fly ash:

5 g of fly ash from a municipal waste incinerator, with a high PCDD/PCDF formation potential were treated with aqueous CuF_2-solution (containing about 100 mg CuF_2) and dried. The mixture was heated in an open glass tube (100 cm, 2.5 cm i.d.) in a stream of oxygen (2 - 20 ml O_2/minute). The cool end of the glass tube was filled with alumina to adsorb any volatilized PFDD/PFDF. Several experiments were carried out, varying the temperature between 250 and 500 °C and the time of treatment between 0.5 and 3 h. The treated fly ash and the alumina adsorbent were extracted under refluxing with a mixture of toluene, ethoxyethanol and HCl. The clean up of the toluene extract was carried out on 25g Alumina B Super I ("macro-alumina column") using 150 ml of heptane/ dichloromethane (98:2) and 150 ml of heptane/dichloromethane (1:1) as eluents.

Pyrolysis of hexafluorobenzene:

30 mg hexafluorobenzene was pyrolyzed in a quartz ampule for 2 h at 250-350 °C. As matrices for the catalysis SiO_2, Al_2O_3, Ni and CuO/Zn were used, respectively.

Pyrolysis of fluortrichloromethan (Freon 11):

2 ml of Freon 11 were heated in a closed quartz ampule (7 cm, 4 cm i.d.) for 1-5 h at 300-600 °C. To catalyze the condensation, different matrices (Al_2O_3, SiO_2, MgO, ZnO) with various concentration of metal (Pt, Ni, Cu, Zn, Fe) were used, respectively.

Burning of Teflon and Teflon containing material:

Teflon and Teflon containing material were placed in a porcelain dish, vaporised, and burnt with a Bunsen burner respectively within 0.5 h. The soot formed was collected on a glass funnel, the tubing of which was filled with alumina as adsorbent. The soot, the adsorbent, and the residue in the dish were extracted with toluene. After clean up of the extract on a "macro-alumina column" analysis for PFDDs/PFDFs was carried out.

Extraction of samples from aluminum production:

Samples from the oven base, dust from the production hall, anode material and a soil sample from the production area were extracted under refluxing with a mixture of toluene, ethoxyethanol and HCl. Clean up was carried out on a "macro-alumina column".

RESULTS AND DISCUSSION

Synthesis of PFDDs and PFDFs:

The various polyfluorinated dibenzodioxins were synthesized by pyrolysis of fluorophenols and fluorophenates according to the synthesis of PCDD [1,2]. By this route were synthesized:

- individual congeners of "symmetrical" substitution, e.g. 2,3,7,8-T_4FDD from 2,4,5-trifluorophenol.
- pairs of products of "asymmetrical" substitution, e.g. 1,2,6,7- and 1,2,8,9-T_4FDD from 2,3,4-trifluorophenol.

- simple mixtures of products of different ring substitution, e.g. from a mixture of 2,3-difluorophenol and 2,3,5,6-tetrafluorophenol a mixture of 1,6- and 1,9- D_2FDD, 1,2,4,6- and 1,2,4,9,T_4FDD, and 1,2,4,6,7,9- and 1,2,4,6,8,9-H_6FDD is formed.
- side products. This is the case for PFDDs which are 1,2,3-substituted, since the corresponding phenols, the 2,3,4,5- and the 2,3,4,6-tetrafluorophenol are not commercially available. These fluorophenols are however present as byproducts in pentafluorophenol. Therefore these 1,2,3-substituted PFDDs could be identified in the pyrolysis product of pentafluorophenol with other phenols.

Various polyfluorinated dibenzofurans were synthesized by pyrolysis of fluorophenols and fluorobenzene or only fluorophenols without fluorine in 2 position.

As in the condensation of PFDDs individual congeners and simple mixtures of PFDFs were synthesized.

The mechanism of the condensations and the product distribution will be discussed elsewhere.

Preliminary toxicological evaluation:

After i.p. injection of male NMRI mice with 100 µg 2,3,7,8-TFDD/kg apparent biphasic kinetics of elimination from blood and liver were obtained. Elimination half-life of 5 minutes (rapid phase) and 165 minutes (slow phase) in blood were calculated. In liver the TFDD level reached a maximum 30 minutes after injection, and also declined in a biphasic manner. For the slow phase of elimination from liver a half-life of ca. 4.5 h was estimated [Figs. 1; 2]. This means a dramatically reduced elimination half-life compared to the chlorinated 2,3,7,8-TCDD (8.5 d) [5]. The rapid phase of 2,3,7,8-TFDD disappearance from blood may be due to a transfer of the compound into the deep compartment, while the slow phase was suggestive of a metabolic degradation or another long-term elimination process.

It was found in previous studies with PCDD and PCDF that there exists a good correlation between the binding to the Ah-receptor, the induction of the Cytochrom (CYP) P4501A1 and the toxic potential [6, 7]. In the very sensitive EROD test the induction of the 7-ethoxyresorufin O-deethylase (EROD) activity can be determined. It is a measure for the P450 1A1 induction [4,8].

In rat hepatocytes in primary culture induction of CYP4501A1-catalyzed EROD activity could be demonstrated indicating that TFDD activates the dioxin receptor. This conclusion was confirmed by studies showing specifically enhanced transcription of a construct containing an XRE (xenobiotic-responsive element) upstream of a heterologous promoter and a report gene [9].

Based on initial concentrations in rat hepatocyte cultures, similar EC_{50} values were found for 2,3,7,8-TFDD and TCDD. These data would allow the calculation of a TCDD equivalency factor (TEF) of ca. 1.0. However, as a consequence of the short half-life of TFDD in mouse blood and liver, the rational basis for the calculation of a TE factor seems to be questionable and has to be extended by further investigations.

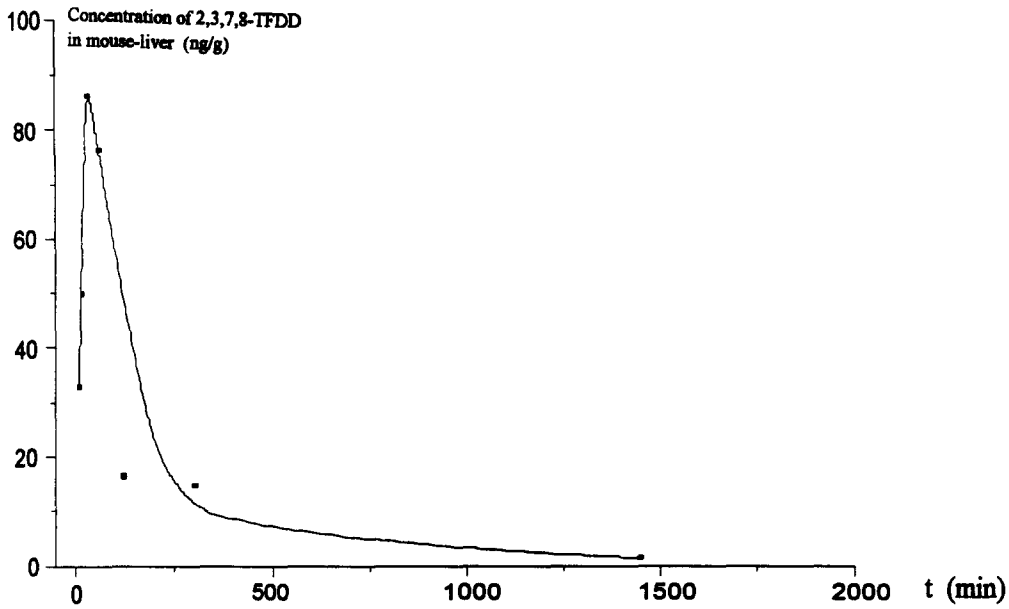

Fig. 1: Time course of 2,3,7,8-TFDD level in liver of male NMRI mice after i. p. injection of a single dose of 100 µg/kg.

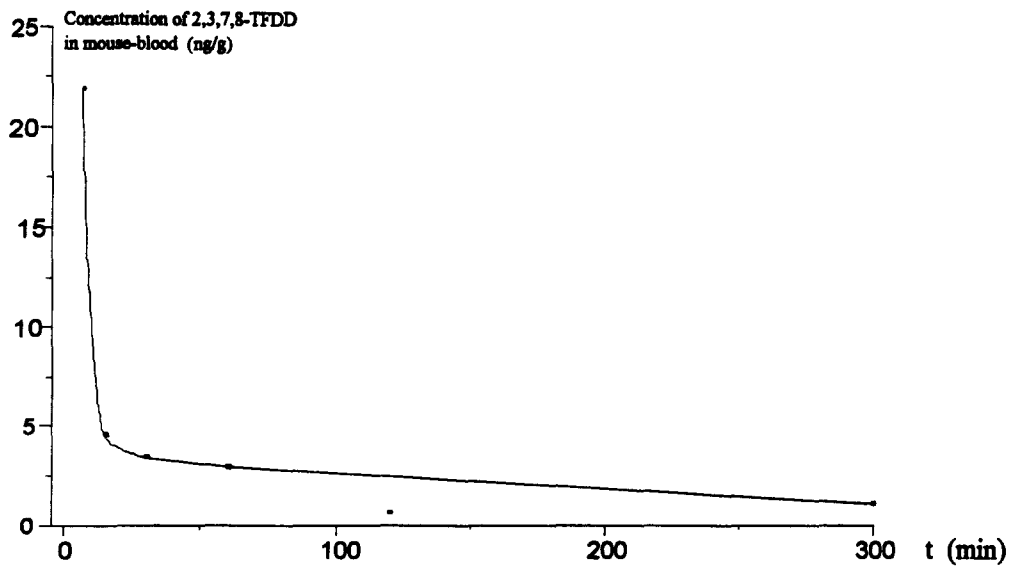

Fig. 2: Time course of 2,3,7,8-TFDD level in blood of male NMRI mice after i.p. injection of a single dose of 100 µg/kg.

Extraction, enrichment and cleaning up from samples containing PFDDs/PFDFs:

So far no significant differences were found in the extraction, enrichment, and clean up of PFDDs/ PFDFs in comparison to the chlorinated analogues in different matrices. Optionally, the PFDDs/PFDFs could be determined together with PCDDs/PCDFs. The main difference is the high volatility of the fluorinated compounds. Therefore it is essential to avoid complete dryness if the solvent is removed during the clean up. For future emission sampling of PFDDs/PFDFs the high volatility of these compounds has to be taken in account.

Separation and identification:

The separation and identification of PFDDs in the pyrolysis products was achieved by HRGC/LRMS. Three capillary columns were tested for highest resolution, DB-5 and DB-5MS, both from J&W, and CPSil-88 from CHROMPACK. The CPSil-88 capillary column was found to be most effective for this purpose, despite the fact, that 2,3,7,8-TFDD overlaps with 1,3,7,9-TFDD. The separation of this pair can however be achieved on a DB-5MS.

All 75 PFDDs and approximately half of the 135 PFDFs could be identified and the retention times relative to dibenzodioxin could be determined [Tab. 1].

The 2,3,7,8 TFDD was characterized also by NMR (^{1}H, ^{13}C, ^{19}F)[Tab. 2].

Mass spectrometric detection of PFDDs/PFDFs:

Fluorine is a monoisotopic element. Therefore, one cannot identify fluorinated compounds in mass spectrometry by isotope clusters in the molecular ion or in fragment ions, as is the case with chlorinated and brominated compounds. The $(M+1)^+$ peak resulting from the ^{13}C-abundance with 13.4% is not very useful for identification purposes. Therefore the mass spectra of the fluorinated dibenzodioxins/furans were examined for characteristic fragment ions [Fig. 5]. Analogous to the characteristic elimination of COCl from PCDDs leading to a $(M-63)^+$ fragment ion, an elimination of COF was found for all PFDDs, leading to a characteristic $(M-47)^+$. Contrary to the PCDDs in PFDDs an elimination of two CO is always observed, resulting in a $(M-56)^+$ fragment ion. This fragmentation is also seen with dibenzodioxin and results in the formation of naphthalene. For the identification of PFDD three ions were always monitored, M^+, $(M-47)^+$ and $(M-56)^+$. M^+, $(M-29)^+$ and $(M-47)^+$ were detected for the identification of the PFDFs. In Figure 3, the full scan mass spectra of 2,3,7,8-TFDD, 2,3,7,8-TFDF, 1,2,3,4,7,8-HFDD and 1,2,3,4,6,7,8,9-OFDF are shown as examples.

Gas chromatographic retention behavior:

With chlorinated, brominated, and mixed chlorinated-brominated dibenzodioxins/furans, retention times on gas chromatographic columns increase with the degree of substitution, independent from the stationary phase. With fluorinated dibenzodioxins/furans, a completely different retention behaviour is observed. The 22 tetrafluorinated dibenzodioxins elute in a rather wide time window. All of the other fluorinated dibenzodioxins elute within this time window of the tetrafluorinated dibenzodioxins. Octa,- hepta-, and most of the hexasubstituted compounds elute early, and most of the mono-, di-, and trisubstituted compounds elute late in this time window, with pentafluorinated compounds also spread out more or less over the total time window of the T_4FDDs. The PFDFs generally elute earlier than the PFDDs, but a few PFDF congeners have longer retention times than the corresponding PFDD congeners. The order of elution of the homologues corresponds with that of the PFDDs. The mass fragmentograms of all the PFDDs and of some PFDFs are shown in Figure 4 and 5.

The reason for the retention behavior is the low polarizibility of the fluorine atoms. The substitution using fluorine atoms also lowers the polarizibility of the whole dibenzodioxin/furan molecule compared to the unsubstituted molecule, which explains the shorter retention times of most PFDDs/PFDFs compared to the unsubstituted

dibenzodioxin. As a consequence, PFDD/PFDF as a whole elute much earlier than PCDD/PCDF. Under the described gas chromatographic conditions, 2,3,7,8 TCDD elutes at 45 minutes. A more detailed discussion of the theoretical aspects of the retention behavior of PFDDs/PFDFs will be reported elsewhere.

Tab. 1: Retention times of the PFDDs relative to Dibenzodioxin (DD)

Congener	Retention time [min]	Retention time in rel. to DD [min]
1,2,3,6,7,8	21,2	-9,7
1,3,6,8	21,3	-9,6
1,2,3,6,8	21,45	-9,45
1,2,3,4,7,8	21,55	-9,35
1,2,3,4,6,8	21,8	-9,1
1,2,3,4,6,7,8	21,85	-9,05
1,2,3,7/1,2,38	22,3	-8,6
1,2,3,4,6,7,8,9	22,35	-8,55
1,2,3,4,7	22,4	-8,5
1,3,7,8	22,5	-8,4
1,2,3,7,8	22,6	-8,3
1,2,3,7,8,9	22,9	-8,0
1,2,3,7,9	23,1	-7,8
1,3,7	23,3	-7,6
2,3,7,8/1,3,7,9	23,4	-7,5
1,2,3,4	23,6	-7,3
1,2,4,7,8	23,8	-7,1
1,3,8	23,9	-7,0
1,2,3,6,7,9	24,1	-6,8
1,2,3,6,8,9	24,1	-6,8
1,2,4,6,8	24,3	-6,6
1,2,4,7,9	24,45	-6,45
2,3,7	24,5	-6,4
1,2,3,4,6,7,9	24,65	-6,25
1,2,3,6,7	24,8	-6,1
1,2,3	25,0	-5,9
1,2,6,8	25,05	-5,85
1,2,4,7	25,1	-5,8
1,2,3,4,6,7	25,25	-5,65
1,2,4,8	25,3	-5,6
1,2,3,6	25,9	-5,0
1,3	26,0	-4,9
1,2,3,4,6	26,1	-4,8
2,7/2,8	26,2	-4,7
1,2,7,8	26,25	-4,65
2,3	26,3	-4,6
1,3,6	26,35	-4,55
1,2,3,8,9	27,0	-3,9
2,3,6	27,1	-3,8
1,2,4	27,3	-3,6
1,2,7,9	27,3	-3,6
1,2,4,6,7,9	27,35	-3,55
1,2,4,6,8,9	27,45	-3,45
1,4,7,8	27,5	-3,4
1,2,7	27,70	-3,2
1,2,3,9	27,8	-3,1
1,2,8	27,9	-3,0
1,2,3,6,9	28,0	-2,9
1,2,3,4,6,9	28,1	-2,8
1,2,4,6,7	28,3	-2,6
1,2,4,8,9	28,3	-2,6
1,3,6,9	28,4	-2,5
2	28,45	-2,45
1,3,9	28,5	-2,4
1,2,6,7	28,75	-2,15
1,7/1,8	28,95	-1,95
1,4,7	29,1	-1,8
1,2,4,6	29,15	-1,75
1,2,4,9	29,25	-1,65
1,2	29,6	-1,3
1,2,6	29,75	-1,15
1,2,4,6,9	30,75	-0,15
1,2,8,9	30,8	-0,1
DD	30,9	0
1	31,3	0,4
1,6/1,4	31,4	0,5
1,2,6,9	31,8	0,9
1,2,9	31,95	1,05
1,4,6	33,0	2,1
1,9	33,2	2,3
1,4,6,9	33,9	3

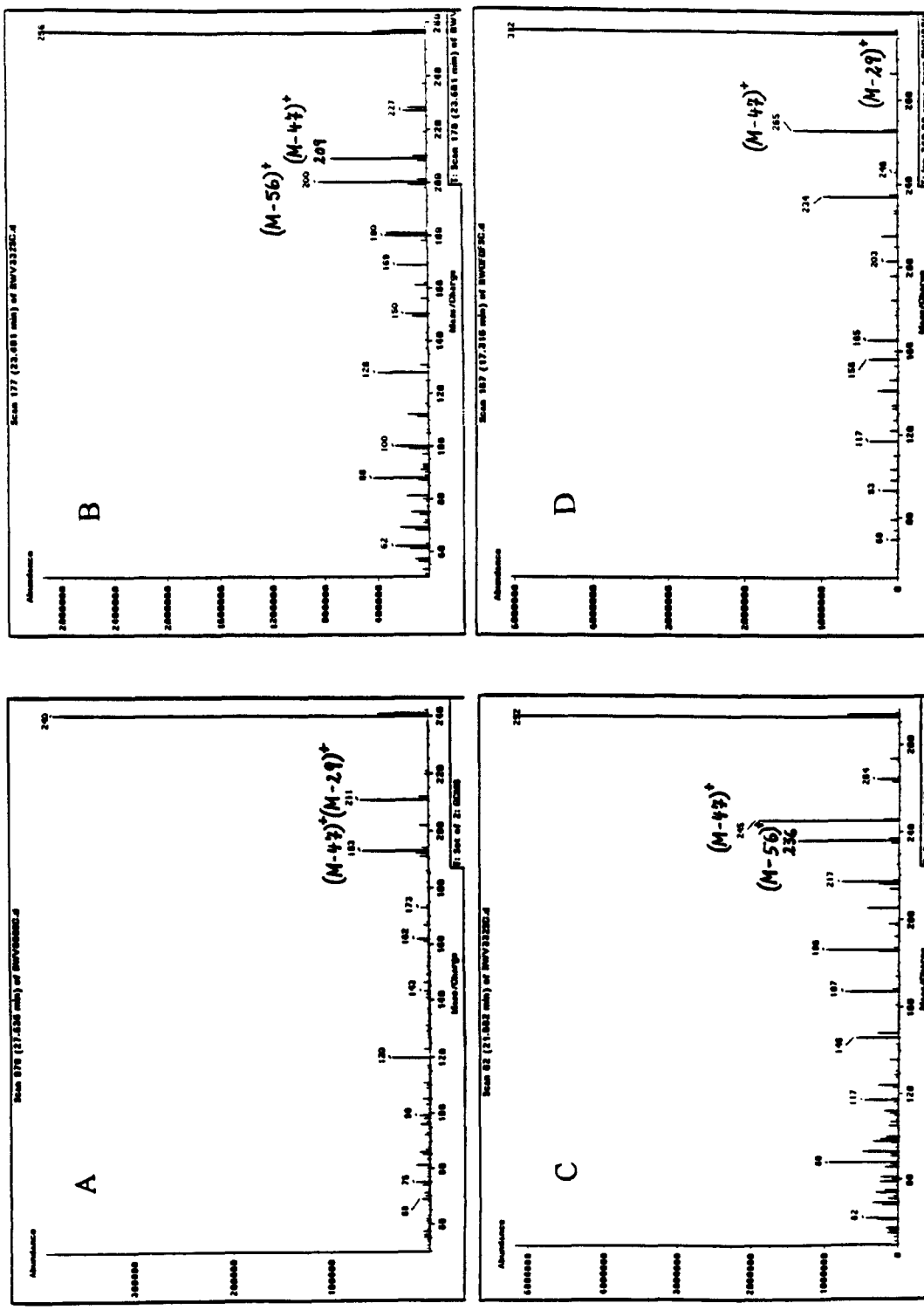

Fig. 3: Mass spectra of some PFDD/PFDF **A**: 2,3,7,8 TFDF; **B**: 2,3,7,8 TFDD; **C**: 1,2,3,4,7,8 HFDD; **D**: 1,2,3,4,6,7,8,9 OFDF

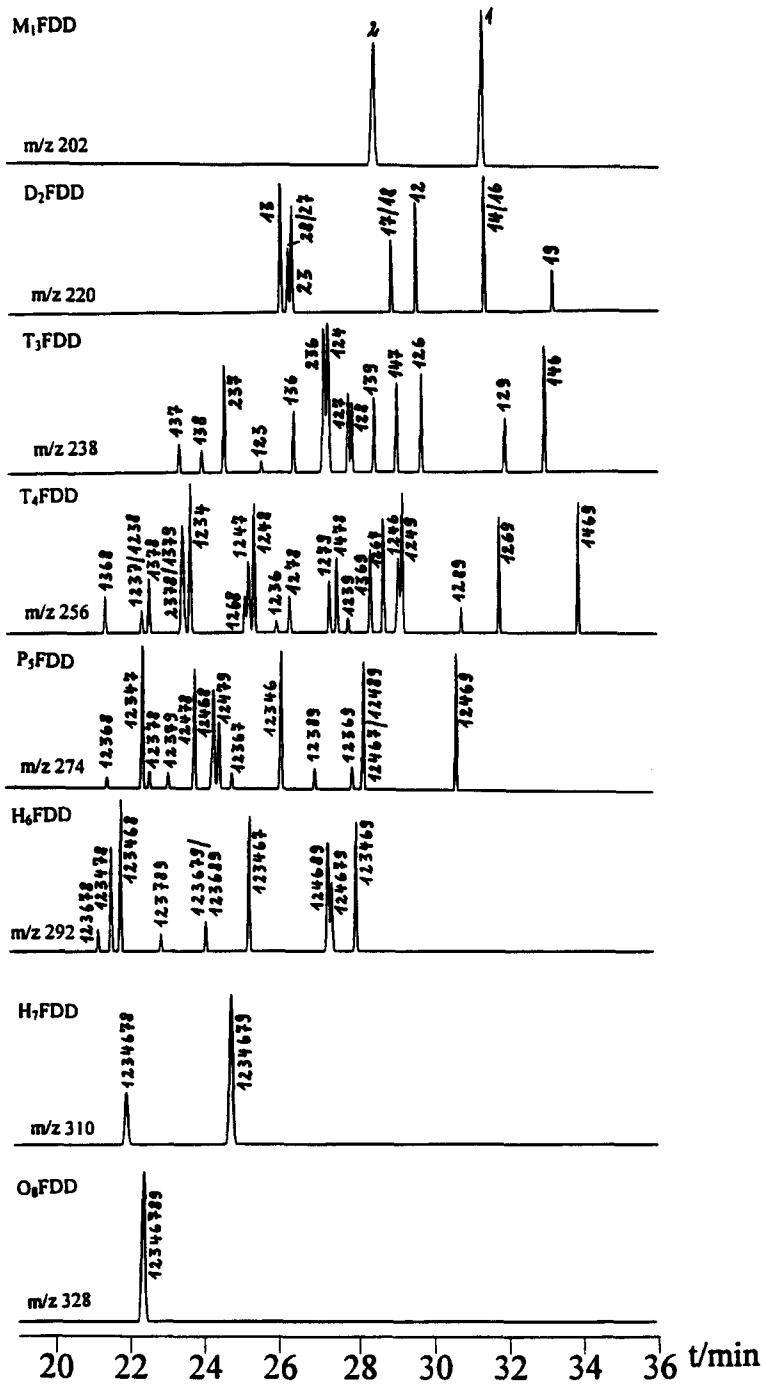

Fig. 4: Reconstructed mass fragmentograms of the mono- to octafluordibenzodioxin

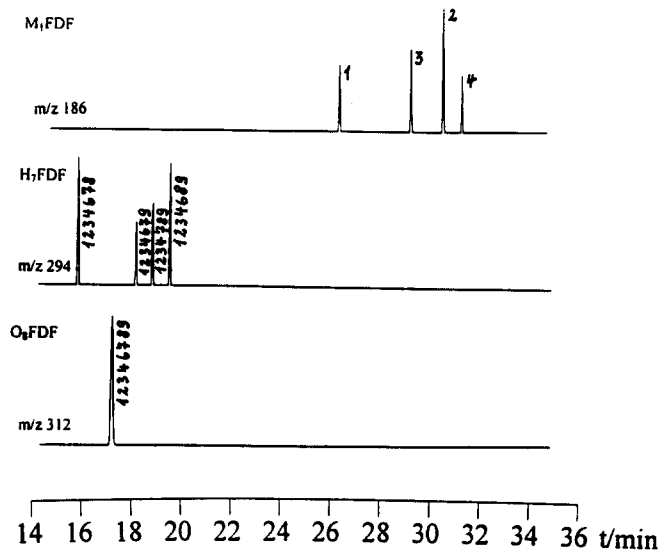

Fig. 5: Reconstructed mass fragmentograms of mono- hepta- and octafluordibenzofurans

Tab. 2: Signals, chem. shift and coupling constants of the NMR-spectra of 2,3,7,8-T_4FDD

spectrum		signal	δ [ppm]	coupling constant [Hz]
^{1}H-NMR	4 äquiv. H	triplet	6,70	$^3J_{H-F} = {}^4J_{H-F} = 8,74$
^{19}F-NMR	4 äquiv. F	triplet	142,30	$^3J_{H-F} = {}^3J_{F-F} = 8,75$
^{13}C-NMR	C at H	double doublet	105,68	$^2J_{C-F} = 13,93$ $^3J_{C-F} = 10,15$
	C at O	triplet	136,87	$^3J_{C-F} = {}^4J_{C-F} = 6,33$
	C at F	double doublet	146,13	$^1J_{C-F} = 246,95$ $^2J_{C-F} = 15,50$

Are PFDDs/PFDFs formed in industrial processes?

Possibility of a *de novo* synthesis in thermal processes:

When fly ash from municipal waste incinerators is heated at 300 °C for 30 min in a stream of air, the concentration of PCDDs and PCDFs increases [10]. This phenomenon has been shown to be caused by a "de novo synthesis" of PCDDs/PCDFs [11]. By the addition of chloride or bromide to the fly ash the heat treatment in an air stream leads to an additional formation of chlorinated or brominated dibenzodioxin and dibenzofuran. When a mixture of CuF_2 and NaF was added to fly ash the subsequent heat treatment in an air stream at temperatures between 300 °C and 500 °C did not result in the formation of fluorinated dibenzodioxins or dibenzofurans. A number of fly ash samples from municipal waste incinerators were analyzed for PFDDs and PFDFs. With detection limits in the range of 0.01 ng/g for individual components no PFDDs/PFDFs could be detected.

The reason for this result is the lack of formation of the C-F bond. It is assumed that for the *de novo* synthesis of PCDDs/PCDFs the formation of Cl_2 is the essential basic reaction, leading to the C-Cl bond formation [11,12,13]. This mechanism is impossible for fluorine due to its redox potential.
Formation of the C-F bond from carbon and metal fluoride occurs only at temperatures above 900 °C [14]. At these temperatures, dioxins are destroyed rather than formed. This might be the reason why in our investigation of samples from aluminum production, despite the formation of C-F bonds no PFDDs/PFDFs and only very low concentrations of PCDDs/PCDFs could be detected.

Possibility of the formation of PFDDs/PFDFs from fluororganic compounds:

Formation of PFDDs/PFDFs from predioxins:

Heating of hexafluorobenzene with various matrices (270-450 °C) leads to varying concentrations of octafluordibenzodioxin/decafluorbiphenylether and octafluordibenzofuran/decafluorbiphenyl.
PFDDs were also found in the fluorophenols, used for synthesizing the PFDDs. The concentrations of the PFDDs were comparable to the concentration of PCDDs found in chlorophenols by Buser.

Possibility of the formation of fluorinated predioxins:

When a stream of fluorotribromomethane is heated (550-750 °C) in a nickel tube, filled with platinum, hexafluorobenzene is formed in about 40% yield [15]. Treating fluorotrichloromethane (Freon 11), a widely used fluorochlorocarbon, under the same condition, no PFDDs/PFDFs could be detected. In burning of Teflon and Teflon containing materials, also no formation of PFDDs or PFDFs could be detected.

The possibility of PFDD/PFDF formation in other processes is under further investigation.

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