Role of electronic factors in the formation of a standard quasi-stable mixture of toxic polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans

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Only electronic factors are responsible for the kinetics and mechanism of consecutive chlorination of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin and 2,3,7,8-tetrachlorodibenzofuran; this results in the formation of a standard quasi-stable mixture of chlorination products (congeners), polychlorinated dibenzo-*p*-dioxins and dibenzofurans, whose composition was independent of the sample type and the place of sampling.

Polychlorinated dibenzo-*para*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) containing chlorine atoms in the 2,3,7,8-positions are extremely toxic substances (the entire group of these compounds is usually referred to as dioxins). The major quantity of these substances is formed as a result of incineration of municipal and hospital wastes and other high-temperature processes in which chlorine-containing substances are produced, destroyed or treated.[1] Because dioxins are a serious hazard to the environment and human health, the mechanism of their formation is studied intensively (see the recent data in ref. 2). Unfortunately, the data acquired hitherto are inadequate to develop the commonly accepted mechanism of the formation and reactions of dioxins because of great experimental difficulties and very expensive analysis for dioxins.

Here a new approach to the elucidation of some details in the mechanism of dioxin formation is suggested. It is based on the analysis of mixtures formed in different sources of contamination. It is believed that, in all cases, the chlorination of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) or 2,3,7,8-tetrachlorodibenzofuran (TCDF) proceeds consecutively with the participation of the same chlorinating agent at all stages of the production of completely chlorinated products. The chlorination path depends on the *ortho*-*para*-directing effects of oxygen and chlorine in the molecule. The quasi-steady-state concentrations of products (congeners) in the mixture formed depend on only the activity of a particular site in the reacting dioxin molecule and the rate of 'discharge' (consumption) of the congener formed.

In the course of a thorough examination of the contamination of human milk with PCDDs and PCDFs in Russia, which was performed within the framework of the WHO programme 'Second Round of Exposure Studies on Levels of PCBs, PCDDs and PCDFs in Human Milk', we found that the composition of PCDD/PCDF contaminants in human milk sampled in different Russian cities was very similar.[3–5] A comparison with the data obtained by other researchers in different countries[6] supported this observation. In this case, the toxicity of milk expressed in the toxic equivalents I-TEQ (*i.e.*, referred to the toxicity of TCDD, which was taken to be unity on the international scale of the equivalent toxicity factors I-TEF) could differ widely (Figure 1). As an example, Table 1 summarises the data for milk from two cities in Russia and for bottom sediment samples from the river of Severnaya Dvina (these data were obtained in different analytical laboratories).

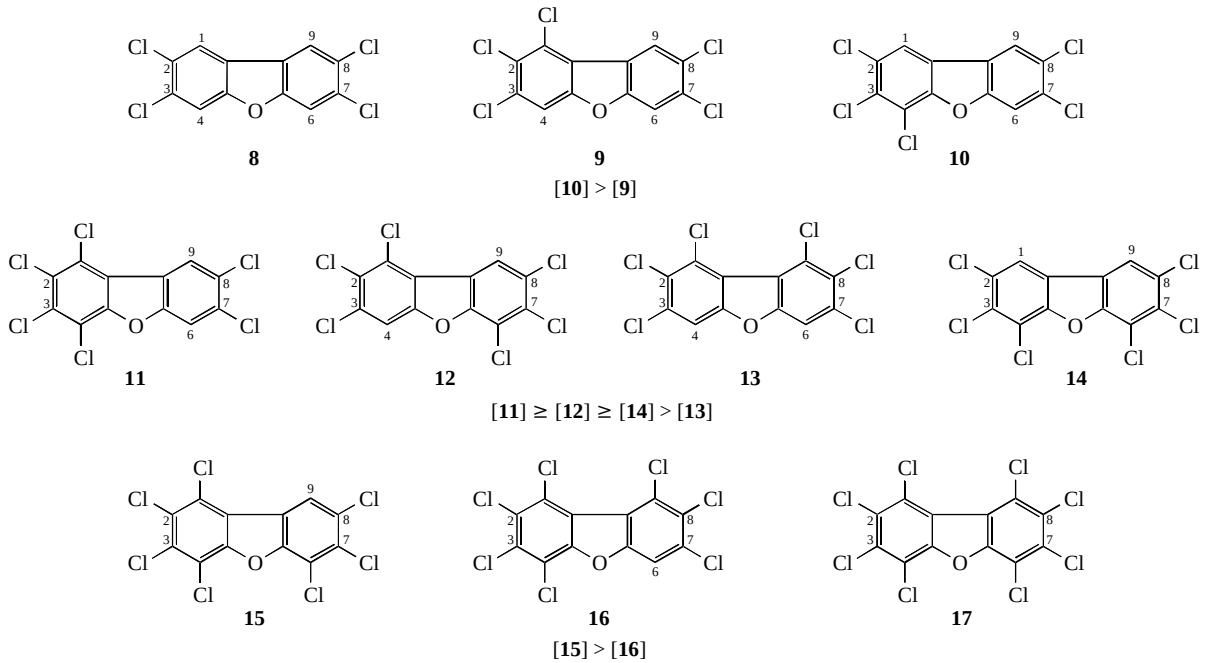
To explain the similar distribution of congeners (not the different TEQ level), we used a mechanism of the consecutive chlorination of aromatic rings in TCDD and TCDF, the precursors of toxic PCDD and PCDF groups, and compared these qualitative data to the experimental data published in terms of 'more–less'. We considered the slopes between two neighbouring points in graphs of the kind shown in Figure 1. The expression of analytical data in terms of molar concentrations did not affect the results obtained. The qualitative composition of the produced mixture can be determined on the basis of simple chemical notions using the model of the formation of a mixture of 17 toxic PCDDs and PCDFs. This approach seems to be very useful taking into account that the analytical data are extremely difficult to obtain.

In this mechanism, TCDD **1** and TCDF **8** (see Table 1 for the compound numbers) are the starting substances. In the consideration of the sequence (probability) of replacement by chlorine in aromatic rings, only a single assumption will be used: the reaction proceeds as usual electrophilic substitution in the aromatic series; therefore, *ortho*-substitution with respect to

Table 1 Dioxin concentrations in human milk[a] (pg per gramm of fat) and bottom sediments from the river Severnaya Dvina[b] (pg kg^{-1}) (data in terms of 10^{-4} pmol g^{-1} for milk and pmol kg^{-1} for bottom sediments are given in parentheses).

Compound	Code	Congener	M_r	Salavat	Volgograd	Severnaya Dvina
1	D_4	2,3,7,8-tetraCDD	322	5.3 (164.6)	2.73	22 (0.068)
2	D_5	1,2,3,7,8-pentaCDD	365.5	3.9 (106.7)	1.47	20 (0.056)
3	D_6(1)	1,2,3,4,7,8-hexaCDD	391	1.0 (25.58)	1.14	39 (0.1)
4	D_6(2)	1,2,3,6,7,8-hexaCDD	391	2.7 (69.05)	3.26	48 (0.123)
5	D_6(3)	1,2,3,7,8,9-hexaCDD	391	0.7 (17.9)	n. d.[c]	40 (0.102)
6	D_7	1,2,3,4,6,7,8-heptaCDD	425.5	3.4 (79.9)	3.98	4420 (0.987)
7	D_8	octaCDD	460	16.4 (356.5)	18.32	3900 (8.48)
8	F_4	2,3,7,8-tetraCDF	306	0.8 (26.14)	1.44	54 (0.18)
9	F_5(1)	1,2,3,7,8-pentaCDF	340.5	0.4 (11.7)	0.62	20 (0.06)
10	F_5(2)	2,3,4,7,8-pentaCDF	340.5	6.9 (202.6)	8.37	17 (0.05)
11	F_6(1)	1,2,3,4,7,8-hexaCDF	375	3.7 (98.7)	4.64	48 (0.13)
12	F_6(2)	1,2,3,6,7,8-hexaCDF	375	2.0 (53.4)	2.32	28 (0.08)
13	F_6(3)	1,2,3,7,8,9-hexaCDF	375	0.7 (18.7)	n. d.	7 (0.02)
14	F_6(4)	2,3,4,6,7,8-hexaCDF	375	0.1 (2.7)	0.82	68 (0.18)
15	F_7(1)	1,2,3,4,6,7,8-heptaCDF	409.5	1.5 (36.6)	1.34	370 (0.9)
16	F_7(2)	1,2,3,4,7,8,9-heptaCDF	409.5	0.1 (2.4)	n. d.	41 (0.1)
17	F_8	octaCDF	444	0.3 (6.76)	n. d.	1100 (2.48)

[a]The data for Salavat (Russia) were obtained in the laboratory of A. K. D. Liem (RIVM, the Netherlands) and for Volgograd (Russia), in the laboratory of W. A. Traag (RIKILT-DLO, the Netherlands). [b]The data (averaged over eight samples) were obtained in the laboratory of N. A. Klyuev (Severtsov Institute of Ecology and Evolution, Russian Academy of Sciences, Russia). [c]n. d. = not detected (the limit of detection was ~0.1 pg per gramm of fat).



Scheme 1 Chlorination of furans (see Table 1 for the numeration of compounds).

the oxygen atom is predominant. Correspondingly, isomers that are formed by *ortho*-substitution will exhibit higher concentrations in the mixture. The consumption of a formed isomer at the following step of chlorination will be considered as a correction factor. The resulting mixture of congeners is considered to be standard (independent of the sources of contamination) and quasi-stable. As an example, we consider the chlorination of TCDF **8** (Scheme 1).

At the first step of the reaction, two pentachloro isomers **9** and **10** can be formed because, in contrast with dioxin **1**, not all positions accessible to chlorination in initial furan **8** are equivalent. Using the accepted model, it is easy to predict that the amount of isomer **10** formed at the first step will be significantly greater than that of isomer **9**. The ratio between these isomers can serve as a measure of the reactivity of the *ortho*-position with respect to oxygen in this system (the 4- and 6-positions) and of the *ortho*-position with respect to chlorine atoms (1- and 9-positions).

To determine the excess of isomer **10** over isomer **9**, the rates of consumption ('discharge') of these isomers at the following step of chlorination should be considered.

Furan **9** has two *ortho*-positions accessible to chlorination, whereas furan **10** has only one position of this kind. Hence it follows that **9** will be consumed at the second step of the reaction more rapidly than **10**. Thus, furan **9** will be formed more slowly and consumed more rapidly than furan **10**. As a consequence, the concentration of furan **9** in the formed mixture of congeners will be lower than that of furan **10**. This conclusion ([**10**] > [**9**]) is supported by data obtained by different authors.

At the third step of chlorination, four hexachloro derivatives of furan (**11**, **12**, **13** and **14**) are formed. Among these compounds, furan **13** can be mentioned. To form **13**, the substitution in the *ortho*-position with respect to chlorine in **9** is required. At the same time, the consumption of **13** is maximally facilitated by two active sites in the 4- and 6-positions. Consequently, among the hexachloro isomers, the rates of formation and consumption of isomer **13** are lowest and highest, respectively, and isomer **13** will exhibit the lowest concentration among all hexachloro isomers. This fact is in complete agreement with analytical data. The formation of isomer **11** also requires unfavourable replacement in the 1-position of isomer **10**. However, isomer **11** will be formed at a higher rate than **13** because, in this case, **11** can also be formed from isomer **9**.

It is evident from a comparison between the rates of formation of isomers **14** and **12** that the formation of **12** is more probable than the formation of **14**: there are two active sites (the 4- and 6-positions) for the formation of **12** from **9** and only a single active site (the 6-position) for the formation of **14** from **10**. Thus, at the stage of production, isomer **13** will be formed in the smallest amount. However, the distribution of the other three isomers is not so obvious, and it is more reasonable to compare the rates of 'discharge' (consumption). Isomer **13** is the most readily consumed, and its concentration in the mixture will be low (see above). This is a good reference compound for testing the model. Isomer **14** is poorly consumed (the two unfavourable 1- and 9-positions); this fact would result in its accumulation. However, this isomer cannot be formed from **9**; consequently, it has only a single channel of formation in contrast with **11** and **12**. Isomers **11** and **12** are not dissimilar in the *ortho*-positions; however, **11** is produced from both of pentachloro isomers **9** and **10**, and **12** cannot be produced from **10**. It is believed that the concentrations of **11** and **12** will be

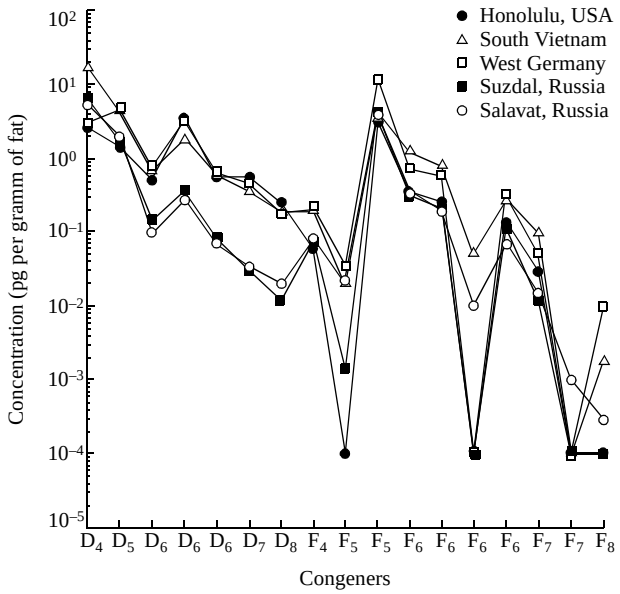


Figure 1 Comparison between the contamination of human milk in different countries, expressed as the toxic equivalents TEQ of the scale I-TEF. The data for Honolulu, Suzdal (Russia) and Salavat (Russia) were taken from refs. 4 and 5, for West Germany and South Vietnam, from refs. 6 and 7. The points at a level of 10^{-4} are below the limit of detection. The codes of congeners correspond to those in Table 1.

not strongly different; however, **11** will be somewhat predominant. Thus, the concentration distribution in the mixture of hexachloro isomers will be as follows: [**11**] ≥ [**12**] > [**14**] > [**13**].

At the fourth step of the reaction, isomer **15** can be produced from three hexachloro isomers **11**, **12** and **14**, and isomer **16**, from isomers **11**, **12** and **13** (the amount of **13** in the mixture is always small). The comparison between the rates of 'discharge' of these isomers shows that isomer **16** will be consumed more rapidly than **15**, which has no free *ortho* 6-position favourable for chlorination. Hence it follows that isomer **15** will be formed more rapidly and consumed more slowly than **16**. Therefore, the concentration of isomer **15** will be higher than that of **16**, which is the case.

As for the concentration of **17**, it will not be used for evaluating the reliability of the mechanism suggested, as is the case with octachloro dioxin **7**. The reason is that concentrations of these compounds, as well as concentrations of tetrachloro isomers **1** and **8**, can vary significantly for unknown reasons.

The same mechanism can also be applied to the chlorination of TCDD.

Thus, the following concentration ratio in the standard quasi-stable mixture of toxic PCDD and PCDF congeners was found:

Dioxins	Furans
[**1**]/[**2**] not found	[**8**]/([**9**] + [**10**]) not found
[**4**] > [**3**], [**5**]	[**10**] > [**9**]
[**6**]/[**7**] not found	[**13**] < [**11**], [**12**], [**14**]
	[**11**] ≥ [**12**] ≥ [**14**] > [**13**]
	[**15**] > [**16**]
	([**15**] + [**16**])/[**17**] not found

For statistical checking, published data on the PCDD/PCDF contamination of various matrices of both biological (blood, milk and foods) and anthropogenic origin (sludge, slimes, bottom sediments, soils, wastewater *etc*.)[8,9] were considered. The total number of analyses was 70; the total number of experimental points was 1190; 910 points were used for comparison with the predicted composition of the mixture. The slopes for the first and last members of the series were not compared because of the absence of data on the initial concentrations. Deviations from the predicted slops were observed for 40 points (4.3%).

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