Gesundheitliche Bewertung dioxinähnlicher polychlorierter Biphenyle in der Innenraumluft

Birger Heinzow

Kiel

5. St. Augustiner Expertentreff 7-2015

Gemischte Gefühle vor dem Einzug

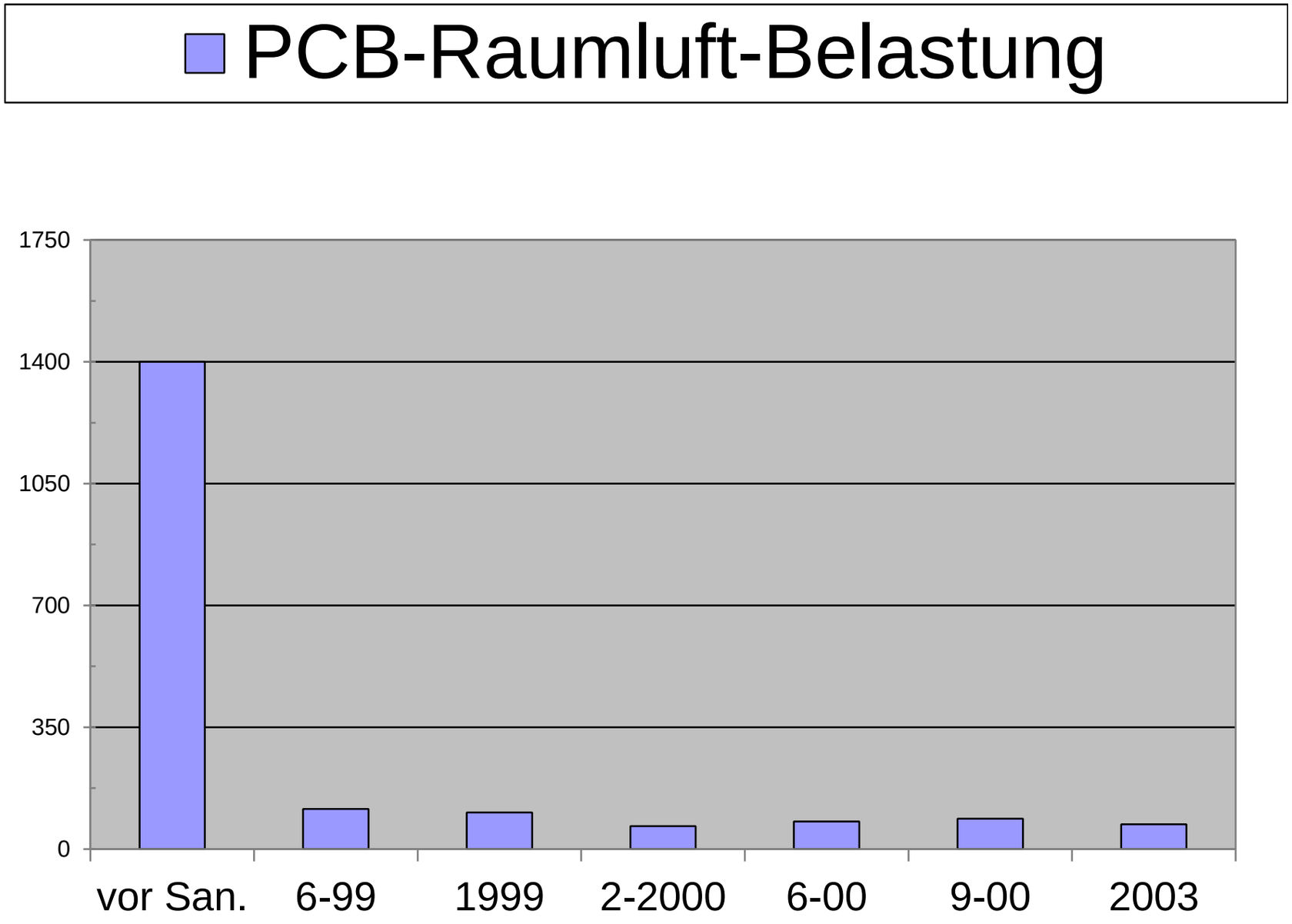
Umweltministerium geht ins Mercatorhaus

Sanierung stieß auf starken Sicherheitsprotest

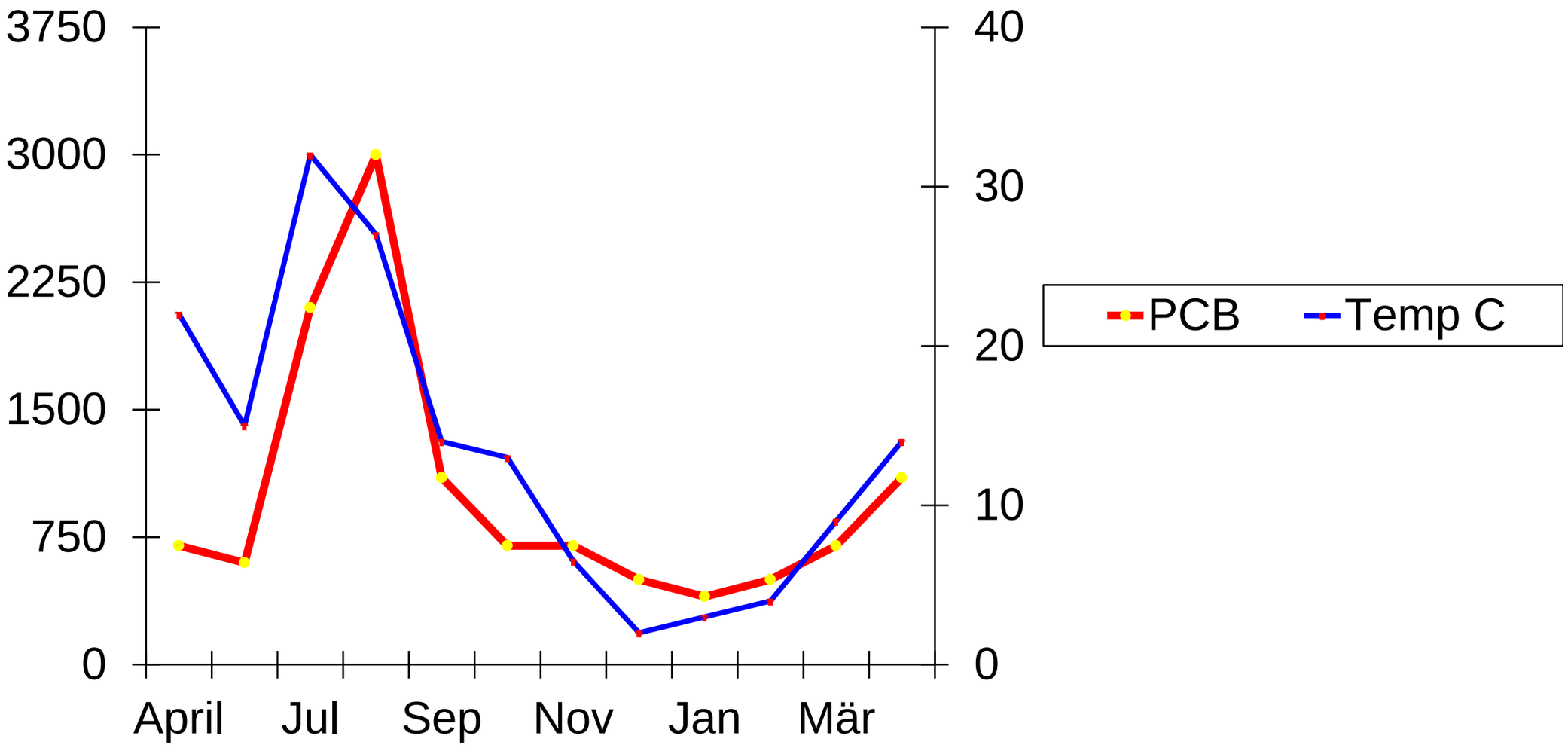
Mit Schutzmaske ins Mercatorhaus

Richtwerte PCB-Richtlinie 1996

- TDI 1 µg/kg/ Tag (=1000 ng/kg KG)
- 60 kg Körper Gewicht
- 20 m³ Atemvolumen / Tag
- 60µg / 20m³ = 3µg/m³
- = <u>3000 ng/m³</u> Eingriffswert
- / 10 (SF)
- = <u>300 ng/m³</u> Vorsorgewert, Zielwert


PCB-Raumluft-Belastung
1750
1400
1050
700
350
0
vor San.
6-99
1999
2-2000
6-00
9-00
2003

Zeitgang Innenraumluftbelastung



PCB – TDI (FAO/WHO), bga 1983

- Pivotal study species : rat
- NOAEL, oral 100 µg/kg bw/day
- Interspecies : 10
- Intraspecies : 10

- **TDI : 1 µg/kg bw/day**

- **Ist heute überholt !**

PCB - RfD (EPA)

- Pivotal study species: rhesus monkey
- LOAEL: oral 5 µg/kg bw/day
- LOAEL to NOAEL : 10
- Interspecies : 3
- Intraspecies : 10

- RfD : 0.02 µg/kg bw/day (Arochlor 1254)

Kritische Effekte an Affen

- Immunotoxische Effekte
- Hauteffekte
- Meibohm Drüsen Inflammation,
- Nagelveränderungen
- ==> ??
- Dioxin Kontamination ?

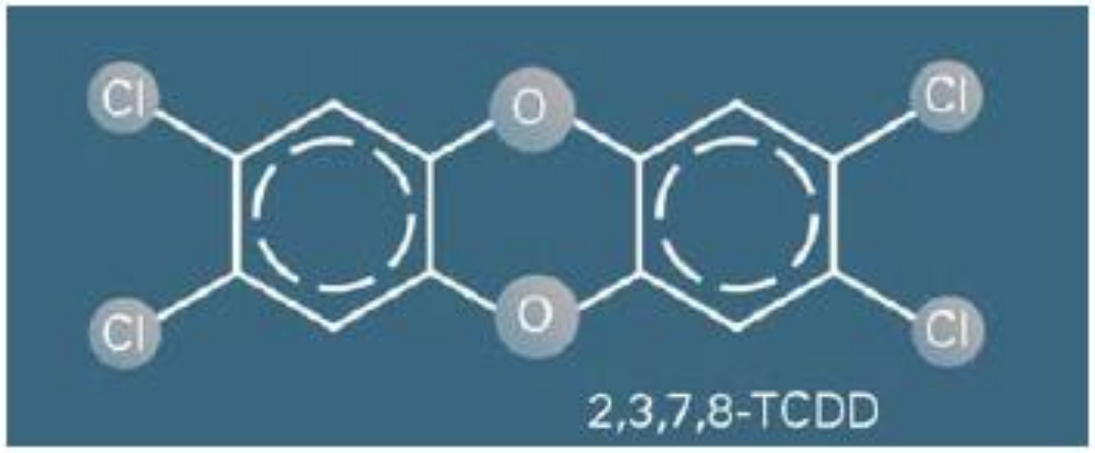
Kritische Studie: Tryphonas et al 1989

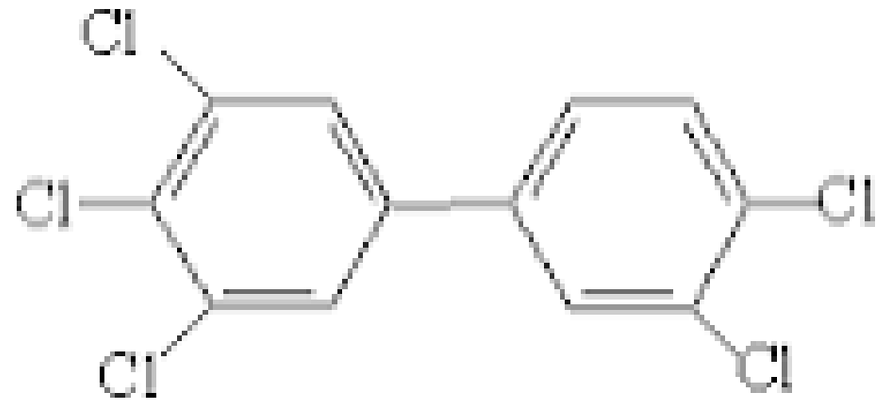
- Arochlor 1254 : 5, 20, 40, 80 µg/kg KG
- LOAEL==> 5 µg/kg bw oral

Kritische Studie: Tryphonas et al 1989

- PCB 1254 Monsanto KA 634
- PCB Mixtur non-ortho = co-planar
- Kongenere + mono-ortho, di-ortho
- => 40 µg TEQ / g PCB 1254 !
- 5 µg PCB/kg bw ==> <u>200 pg TEQ/kg bw</u>
- > LOAEL TEQ
- *SCF 5-20-2001*

dl-PCB





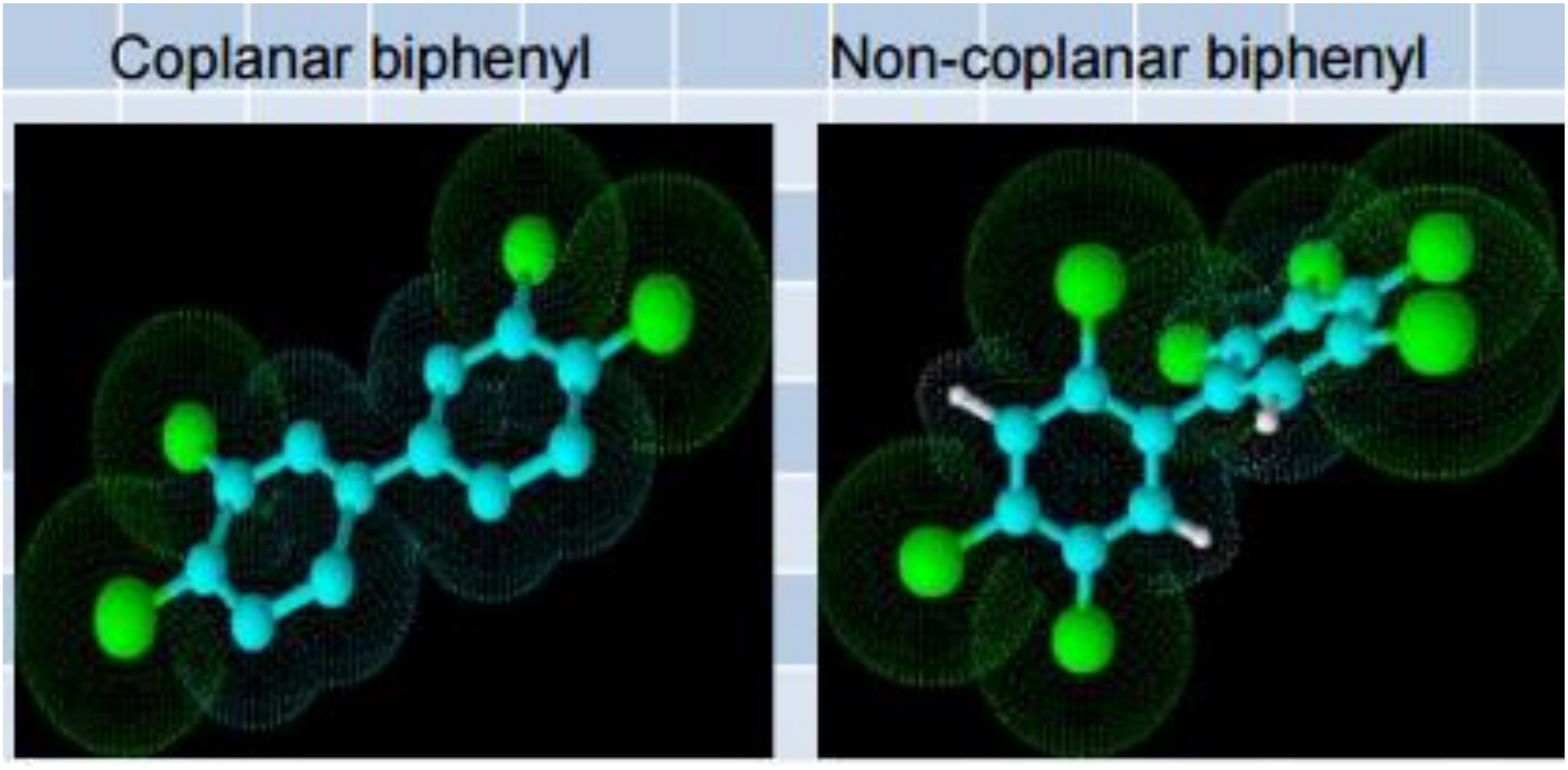
„dioxine-like" : z.B. **PCB 126**

Struktur

Wirkung

tox. Endpunkte

dl- / ndl-PCB



Grafik: IARC

Bewertung über TEQ (WHO)
analog zu „Dioxinen"

Dioxinähnliche PCBs nach WHO :

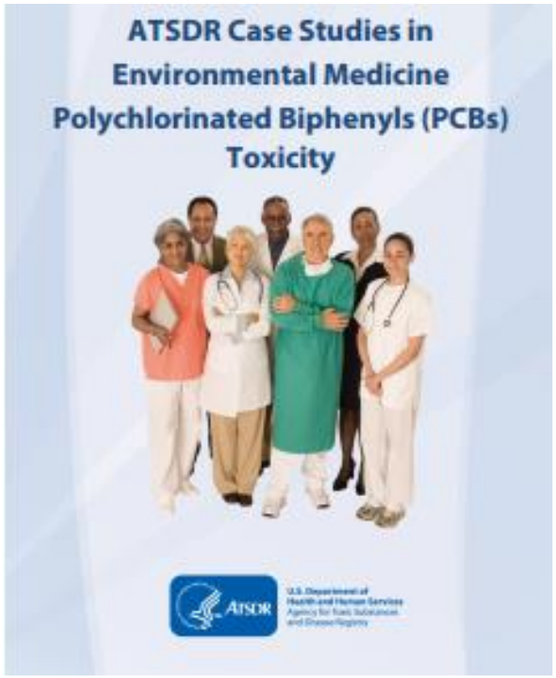
non-ortho PCBs: PCB 77, 81, 126 und 169

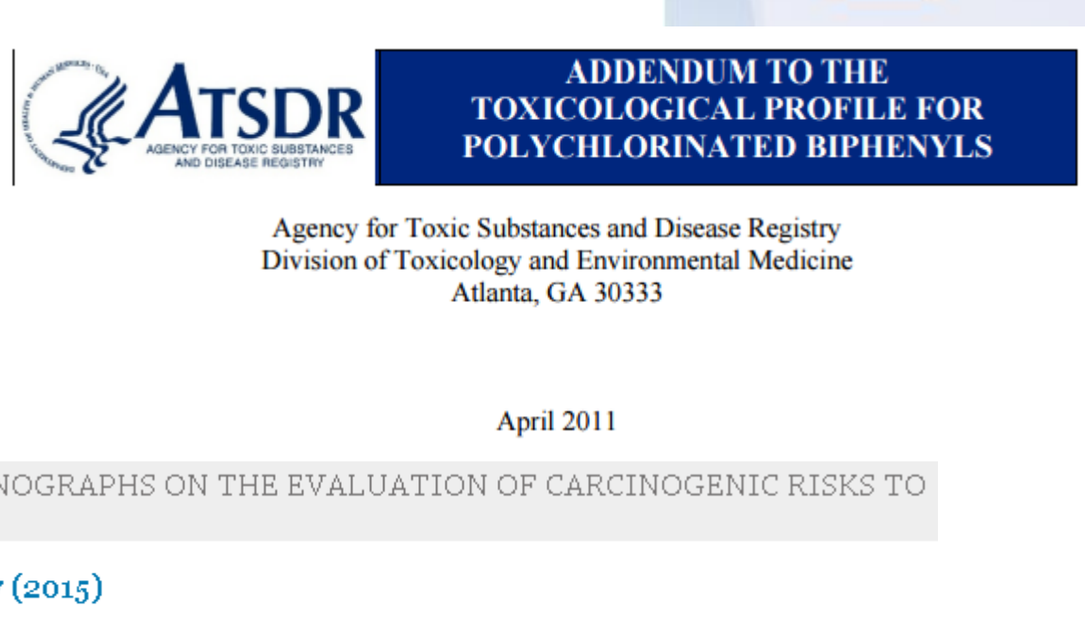
(= koplanare PCB)

mono-ortho PCBs: PCB 105, 114, 118, 123, 156, 157, 167 und 189

Toxikologie PCB, Dioxine

- **Exposition immer als** Gemisch
- **Wirkung vielfältig u.a. :**
- Dermatotoxisch
- Hepatotoxisch
- Immunotoxisch
- Neurotoxisch
- Endokrine Disruption
- Entwicklungstoxizität
- Kanzerogen (IARC 1)




ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR POLYCHLORINATED BIPHENYLS

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
Atlanta, GA 30333

April 2011

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

Volume 107 (2015)

Polychlorinated Biphenyls and Polybrominated Biphenyls

http://monographs.iarc.fr/ENG/Publications/techrep42/TR42-17.pdf
http://monographs.iarc.fr/ENG/Monographs/vol107/index.php

http://monographs.iarc.fr/ENG/Publications/Review2014-MechanisticData-Beatrice.pdf

Key role of mechanistic data in recent evaluations of TCDD, PCBs and PBBs

Béatrice Lauby-Secretan, on behalf of the *IARC Monographs* Programme

Cancer in humans

	TCDD	PCBs	PBBs
Cohort study populations	• Occupational settings (US NIOSH study; BASF cohort; IARC multicountry cohort) • Accidental exposure of the general population (Seveso, Italy)	• Occupational settings (n=13) • Accidental exposure of the general population (Yusho, Yucheng) (n=4) • Populations with high dietary exposure (n=5) • General population (n=15)	• Accidental exposure of the general population (Michigan, USA) (n=1)
Case–control studies	• Nested case–control studies within the IARC cohort for soft-tissue sarcoma and NHL	• cancer of the breast (n=32) • NHL (n=17) • Other sites (n=9)	N.A.
Sites with sufficient evidence in humans	• All cancers combined	• Cutaneous melanoma	N.A.
Sites with limited evidence in humans	• Lung • Soft-tissue sarcoma • NHL	• NHL (clear dose–response in several studies) • Breast	N.A.
Other positive findings	N.A.	• Dose–response for cancers of the brain, prostate, stomach, and pancreas	• Combined digestive system (excluding colon and rectum) • Lymphoma

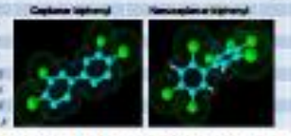
Overall evaluations

Agent	IARC Group	Volumes
2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD)	1	15, 41, 69, 100F
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)	1	100F
Polychlorinated biphenyls, dioxin-like, with a Toxicity Equivalency Factor (TEF) according to WHO (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189) NB: Overall evaluation, upgraded to Group 1 with strong supporting evidence from mechanistic data	1	100F
Polychlorinated biphenyls	1	18, 107
Polybrominated biphenyls NB: Overall evaluation, upgraded to Group 2A with supporting evidence from mechanistic data, namely mechanistic similarity with polychlorinated biphenyls	2A	18, 107

Cancer in experimental animals

	TCDD	PCBs: individual congeners, binary mixtures, and fresh commercial products	PBBs: individual congeners and fresh commercial products
Rat	Liver, biliary tract, lung, oral mucosa, hard palate /turbinates, tongue, thyroid gland, subcutaneous tissue, adrenal gland, pituitary gland, uterine cervix, pancreas, skin	Liver, biliary tract, lung, oral mucosa, thyroid gland, uterus Offspring: mammary gland (benign + malignant)	Liver, biliary tract, myelomonocytic leukaemia, mononuclear cell leukaemia
Mouse	Liver, lung, thyroid gland, lymphoma, subcutaneous tissue	Liver, lung, skin (topical) Offspring: promotion of lung tumours	Liver, thyroid gland; promotion of liver tumours

Chlorine position on the biphenyl rings and congener nomenclature (BZ)



Dioxin-like PCBs (with a Toxic Equivalent Factor) are highlighted in red.

Mechanistic data relevant to the carcinogenic potential of PCBs and PBBs

Coplanar and non-coplanar biphenyls

Non-coplanar biphenyls		Coplanar biphenyls
CAR/PXR	Target receptor	AhR
CYP2B1/2	Induction of xenobiotic-metabolizing enzymes	CYP1A1
Mutations, DNA strand-breaks, chromosomal aberrations	Genetic and related effects	DNA-adduct formation
Liver	Organ toxicity	Liver, skin
Metabolic activation and other mechanisms	Immunotoxicity	AhR-mediated
Driven by hydroxylated metabolites	Endocrine effects	AhR-mediated (steroid hormones)
Carcinogenic potential		
Cross potentiation of coplanar and non-coplanar biphenyls in combined carcinogenesis bioassays		

Upgrading PBBs based on similarities with PCBs

- Several shared chemical and physical characteristics
- Effectively absorbed and distributed across the placenta and detected in milk
- Long estimated half-lives in animal tissues, serum and fat
- Potent and efficacious inducers of xenobiotic–metabolizing enzymes
- Individual PBB congeners inhibit cell to cell communication or metabolic cooperation
- Individual PBB congeners are weak initiators and strong promoters of two-stage hepatocarcinogenesis
- Ligands for several cellular and nuclear receptors
- Pathological and biochemical changes in the liver and thymus within days in studies of acute exposure
- In studies of chronic exposure in rodents, microscopic changes in the liver, bile-duct proliferation, and mild microscopic changes in thyroid glands
- Reduced immunocompetence following PBB exposure in rodents, birds, cattle, swine, and humans
- Perinatal exposure in rats to PBBs diminished the effect of estradiol administered exogenously on uterine weight and uterine RNA content
- Increased microsomal metabolism of estradiol, estrone and ethynylestradiol *in vitro*
- Increased odds of a male birth following PBB exposure in women

Historical perspective

- Since 1977, the *IARC Monographs* Programme has conducted several evaluations of the carcinogenic hazards of dioxins, polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) (see overall evaluations).
- In October 2009, in the frame of the re-evaluation of 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) in volume 100F, PCB 126 was upgraded to Group 1 and the Working Group recommended an in-depth re-evaluation of agents with properties similar to TCDD.
- In February 2013, the *Monographs* programme conducted a re-evaluation of PCBs and PBBs.

OUTCOME AND IMPACT OF THE EVALUATIONS

- ✓ PCBs identified as priority agents in 2009 (IARC Technical Publication No. 42-*Identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens*, 2009)
- ✓ *IARC Monographs* volume 107 meeting on PCBs and PBBs publicized to the scientific community through an oral presentation (7th *International Workshop on PCBs*, Arcachon, France, May 2013)
- ✓ Contribution to the report by the Danish Health and Medicines Authority "*Health risks of PCB in the indoor climate in Denmark*" (in press)
- ✓ Publication of the outcome shortly after the meetings :
  - Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Galichet L, Cogliano V (2009). Lancet Oncol 10,1143-4
  - Lauby-Secretan MB, Loomis D, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K (2013). Lancet Oncol, 14, 287-8

HOW MECHANISMS COME INTO PLAY

- ✓ TCDD was the 2nd carcinogen to be classified in Group 1 without sufficient evidence in humans, on the basis of strong mechanistic data; first subsequently confirmed by sufficient evidence *in humans*.
- ✓ PCB126 upgraded to Group 1 on the basis of extensive evidence showing activity identical to TCDD for every step of the mechanism described for TCDD-associated carcinogenesis in humans
- ✓ "Dioxin-like" PCBs upgraded to Group 1 on the basis of evidence showing activity similar to TCDD, and as a class of compounds similar to PCB126
- ✓ "HOWEVER, the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs."
- ✓ PBBs upgraded to Group 2A with mechanistic data, based on strong similarities with PCBs.
  - ➢ **Cascade of evaluations of individual compounds that have similarities in their biological activities, leading to a higher classification based on strong mechanistic evidence**

International Agency for Research on Cancer
World Health Organization
http://monographs.iarc.fr

The *IARC Monographs* Programme staff

Acknowledgements

Financial support was received from:
- US National Cancer Institute (Cooperative Agreement 5-U01-CA33193)
- US NIEHS/National Toxicology Program
- European Commission (DG Employment, Social Affairs and Inclusion)

Bekanntmachung

Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz 2007 · 50:
DOI 10.1007/s00103-007-0377-5

Gesundheitliche Bewertung dioxinähnlicher polychlorierter Biphenyle in der Innenraumluft

Mitteilungen der Ad-hoc-Arbeitsgruppe der Innenraumraumlufthygiene-Kommission des Umweltbundesamtes und der Obersten Landesgesundheitsbehörden

Grafik : BGesBl.2007

Schwelleneffekte?
Ja oder Nein

- **Nein:** genotoxische Substanzen, stochastische Effekte, kein Nullrisiko
- **Niedrig #** : Rezeptorvermittelte, nicht genotoxische Substanzen
- **Ja #** : nicht-genotoxisch, epigenetisch/ zytotoxische Substanzen

  – **#** Schutz durch NOAEL oder BMD/SF-Konzept :

→ **RW-Wert-Ableitung vertretbar**

Richtwert-Ableitung ad-hoc AG

- Analog zum europäischen Lebensmittelbereich
- Bezug sind dioxinähnlichen Wirkungen sowohl der polychlorierten Dibenzodioxine (PCDD) und Dibenzofurane (PCDF) als auch der dl-PCB
- **POD:**
- **LOAEL** für empfindliche Personen von **6 pg TCDD** bzw. TEQ/kg Körpergewicht und Tag
- Resorbierte Dosis (50%) = 3 pg / kg(KG) Tag
- - Hintergrundbelastung 1,5 pg / kg(KG) Tag

TEQ IRL-RW II

- **1,5 pg/kg KG** Rest für Inhalationspfad →
- Atemrate 0,3 m³ /kg(KG)Tag
- 1,5 pg/kg(KG) Tag / 0,3 m³/kg(KG) Tag
- **= 5 pg/m³**
- **?**
- **Einhaltung TEQ-RW / Σ-PCB-RW**

typische Quellen für PCB IRL-Belastungen:

u.a. Flammschutzanstriche, Dichtungsmassen

==> PCB A 30 - A 60 „Fingerprint“

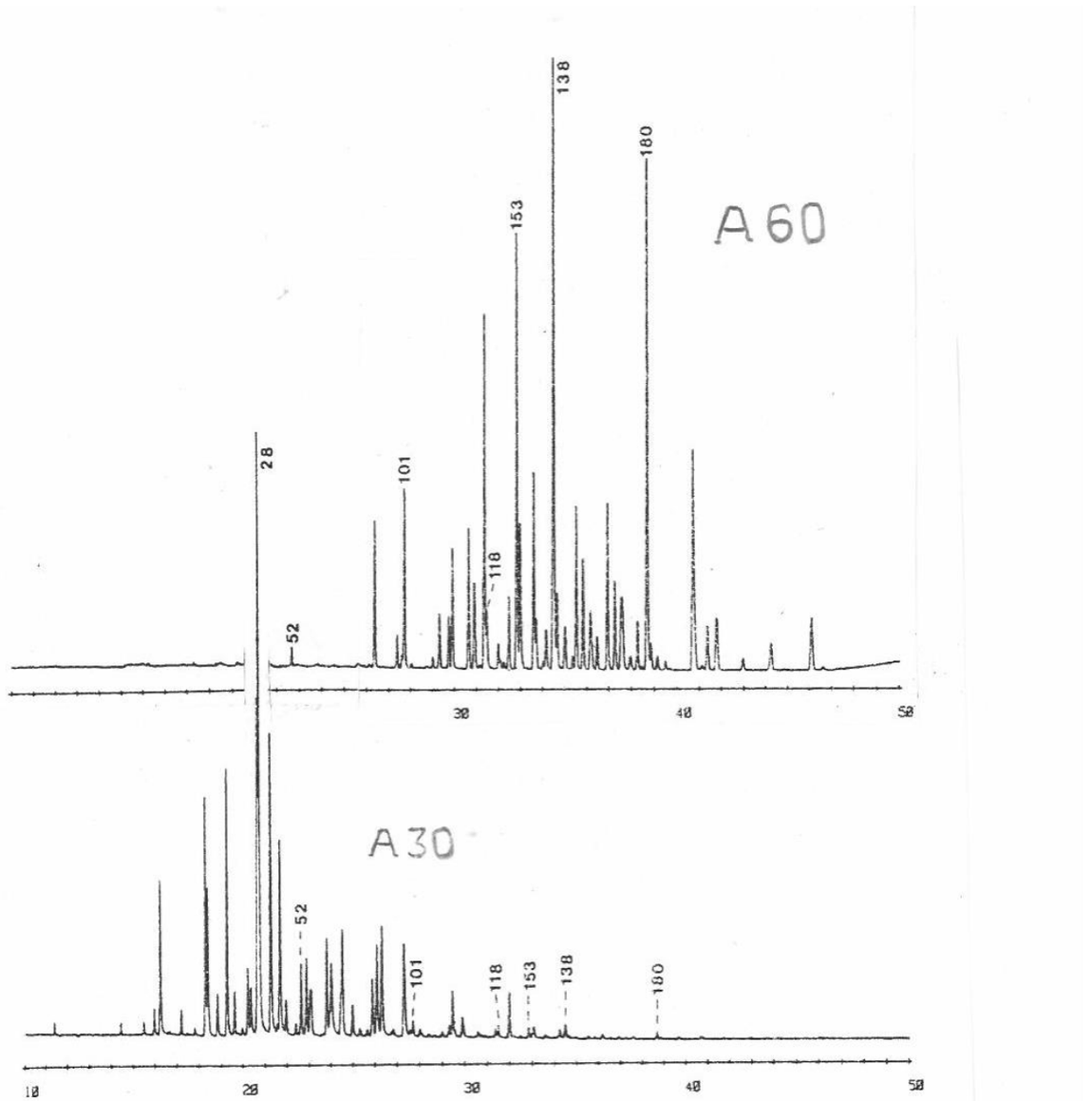
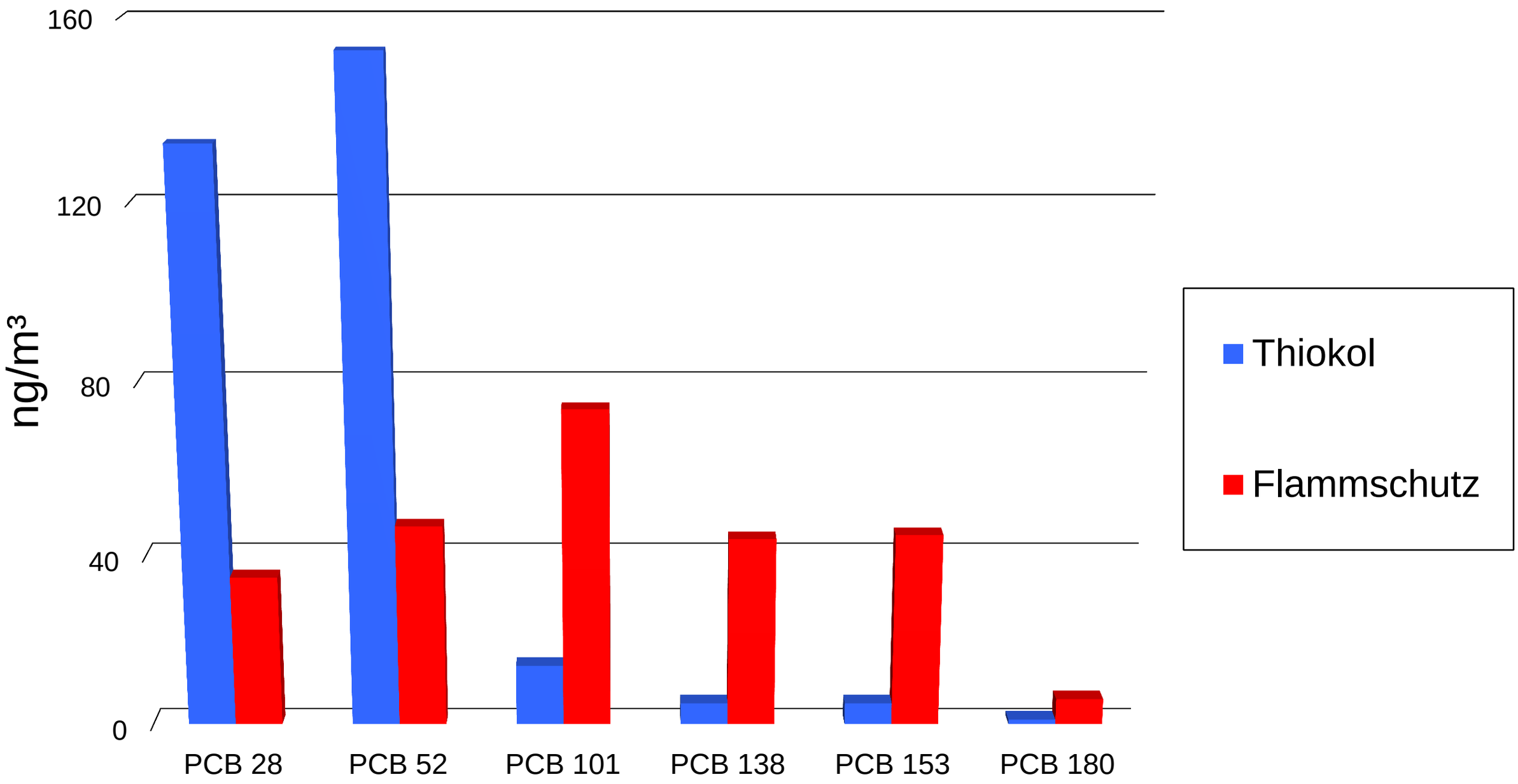


Abb. 2: Gaschromatogramm von Clophen A 30

Muster der DIN PCB-Kongenere

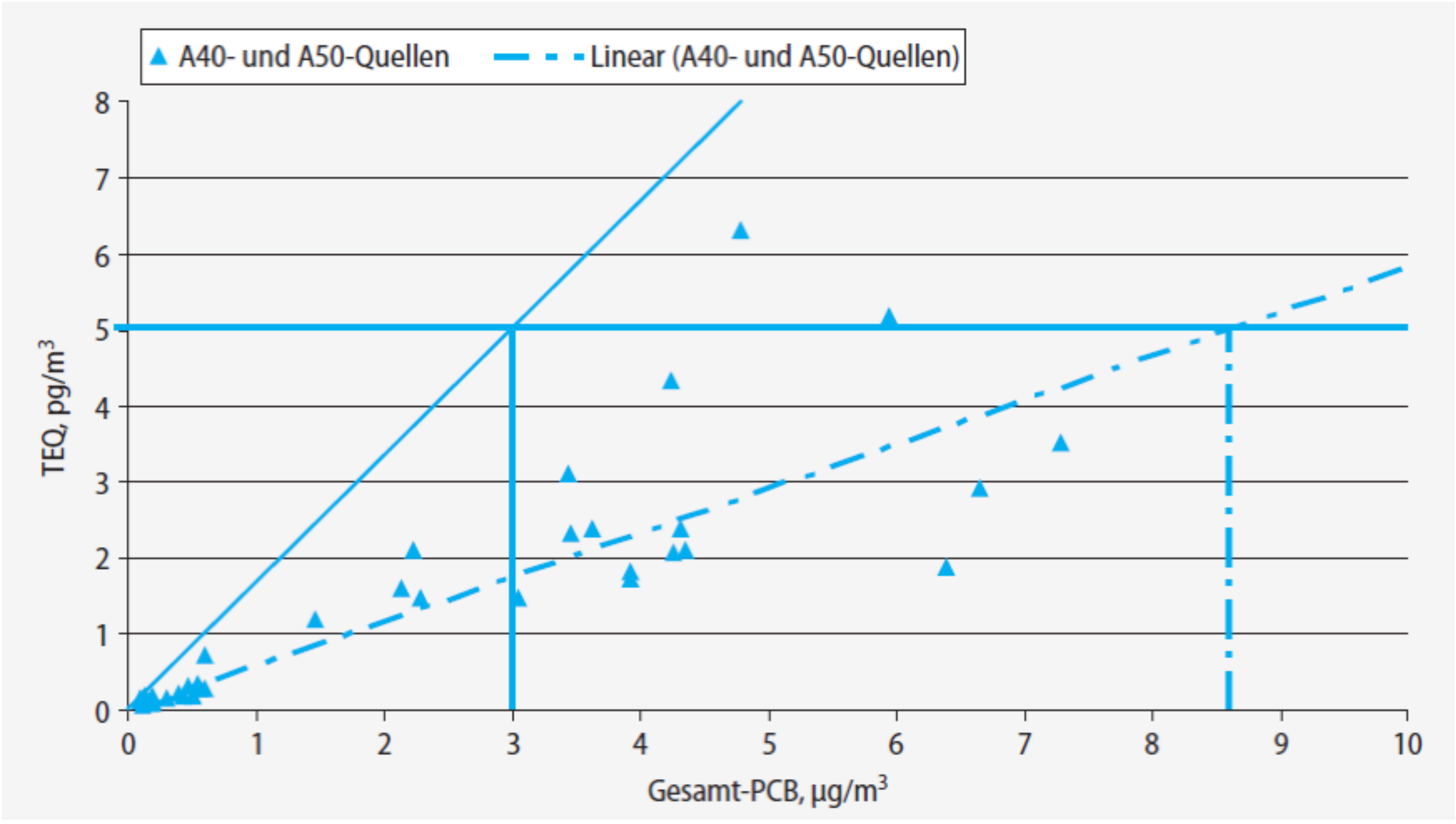


IRL-Belastung aus untersch. Quellen

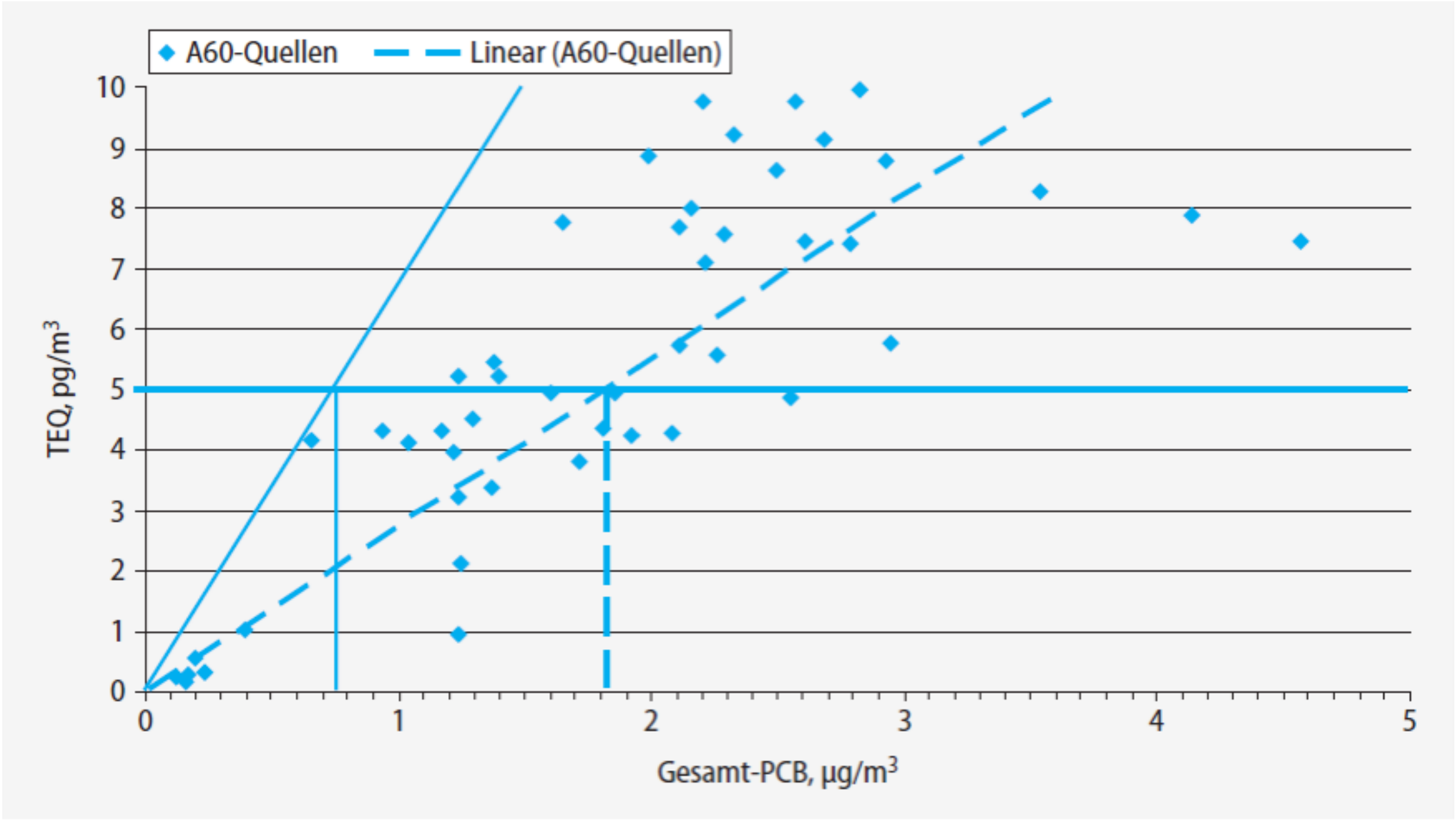
Quelle	Σ-PCB (ng/m³) (5x6 DIN-PCB)	PCB-TEQ (pg/m³)	Total-TEQ (pg/m³)
Thiokol	1400	0.57	0.61
Flamm-schutz	1300	3.4	3.8

- **Σ-PCB schlechter Schätzer der TEQ !**

PCB-TEQ-Konzentration **/PCB A40 -A50 Quelle**

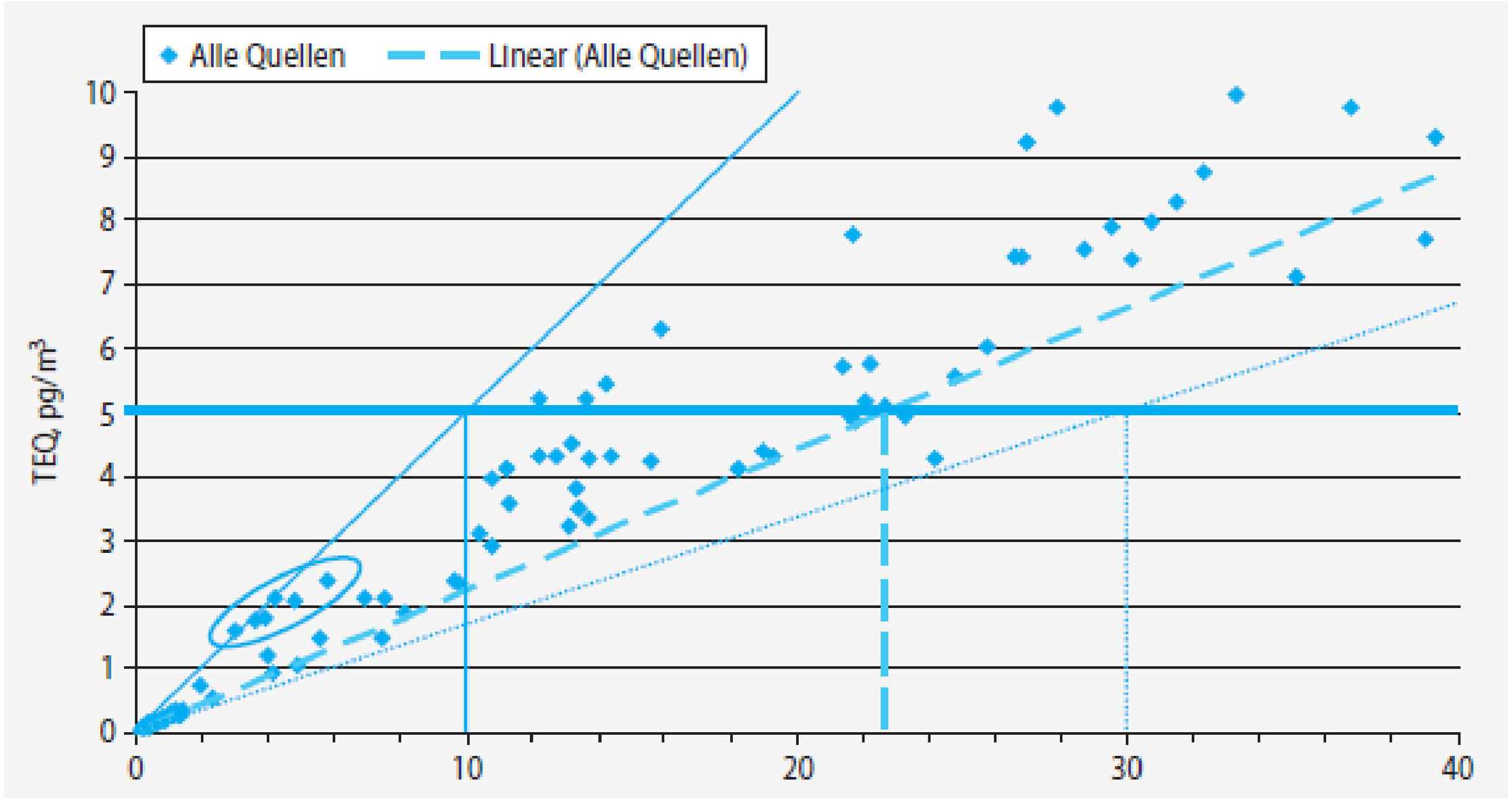


PCB-TEQ-Konzentration /PCB A60 Quelle



Grafik : BGesBl.2007

PCB-TEQ-Konzentration / PCB 118 Leitkongener



Grafik : BGesBl.2007

Prüfwerte für PCB IRL-Belastungen

- Einsatz der Prüfwerte ist konservativ mit ausreichender Sicherheitsspanne

- Konzentration unter **1 µg Σ-PCB/m³**
  ==> TEQ-Wert **5 pg/m³** mit hoher Wahrscheinlichkeit unterschritten

- Konzentration unter **10 ng PCB 118/m³**
  ==> TEQ-Wert von **5 pg/m³** sicher eingehalten!

Aachener Empfehlungen

- Nicht mehr im belasteten Gebäude eingesetzt:
- Schwangere
- Beschäftigte mit schweren chronischen, das Immunsystem schwächende Erkrankungen oder unter Immunsuppression
- Beschäftigte, die sich gesundheitlich gefährdet fühlen oder sehr ängstlich reagieren

- Besondere Beratung von Frauen im gebärfähigen Alter im Hinblick auf Kinderwunsch

http://sundhedsstyrelsen.dk/publ/Publ2013/12dec/HAofPCBindoorDK_en.pdf

HEALTH RISKS OF PCB IN THE INDOOR CLIMATE IN DENMARK – background for setting recommended action levels

2013

Background report prepared for DHMA by Nordic Institute of Sustainable Products and Environmental Chemistry and Toxicology