PCB : meccanismi di tossicità e superamento del concetto di tossicità equivalente ?

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Direttore UO Medicina del Lavoro Igiene Tossicologia ,
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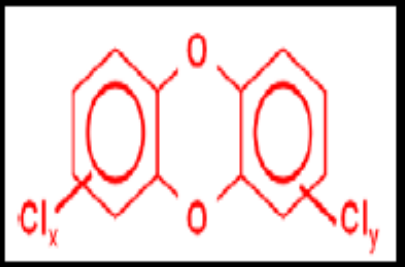
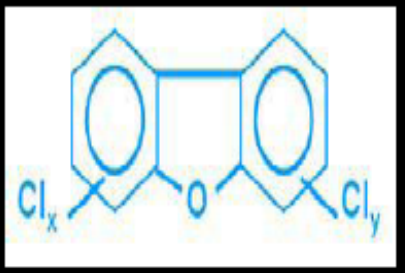
Criteri di Bradford Hill

- **Forza dell'associazione** (un elevato rischio relativo è verosimilmente meno spiegabile da bias)
- **Consistenza** (in differenti popolazioni in differenti circostanze)
- **Specificità** (causa singola – effetto singolo)
- **Temporalità** (la causa precede l'effetto)
- **Gradiente biologico** (presenza di una relazione dose-risposta)
- **Plausibilità biologica** (conoscenza di meccanismi biologici)
- **Coerenza** (tra tipi diversi di evidenza)
- **Evidenza sperimentale** (con variazione del solo fattore d'interesse)
- **Analogia** (tra risultati simili)

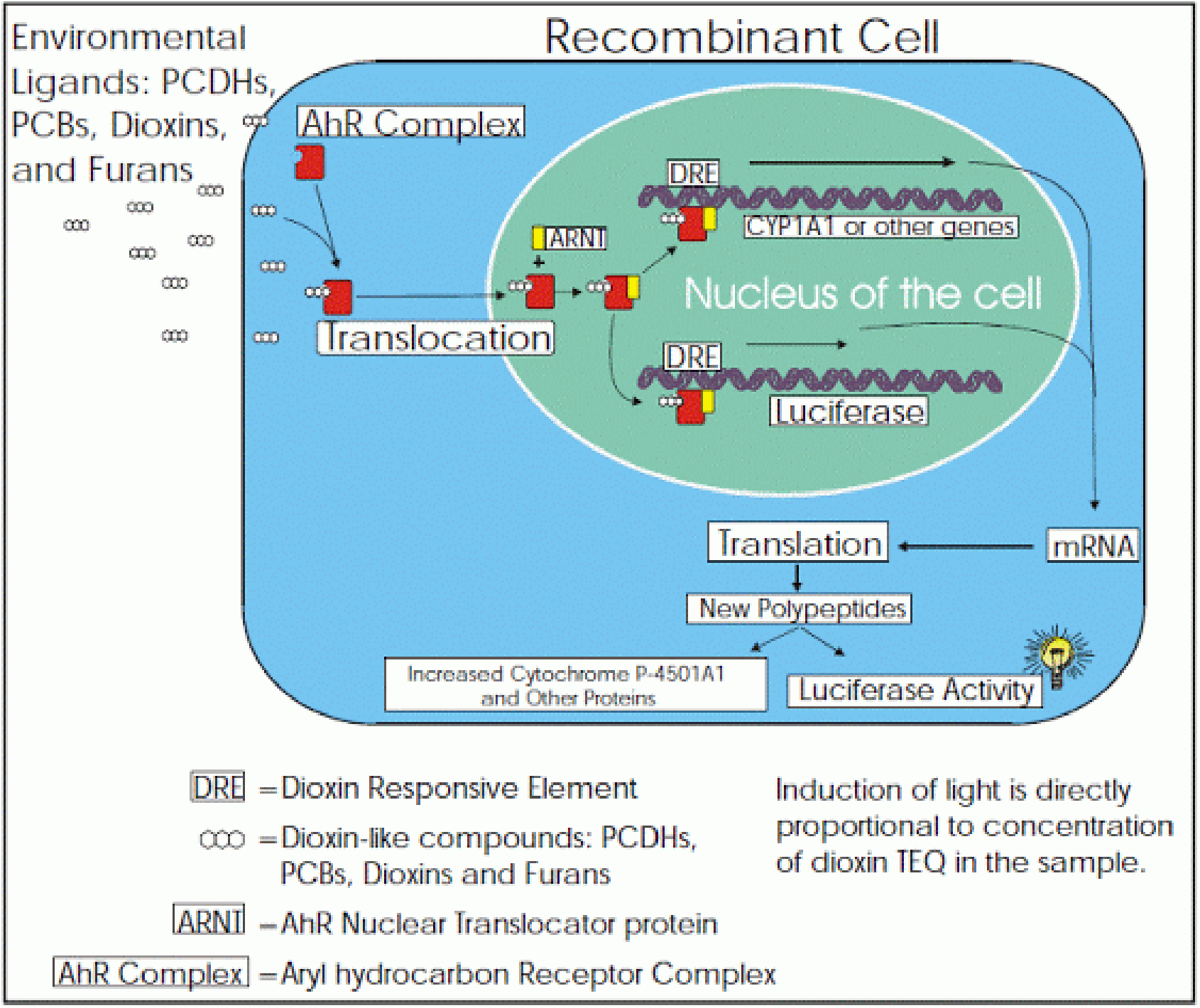
Nome	Struttura	Congeneri	Congeneri tossici
PCDDs		75	7
PCDFs		135	10
PCBs		209	12

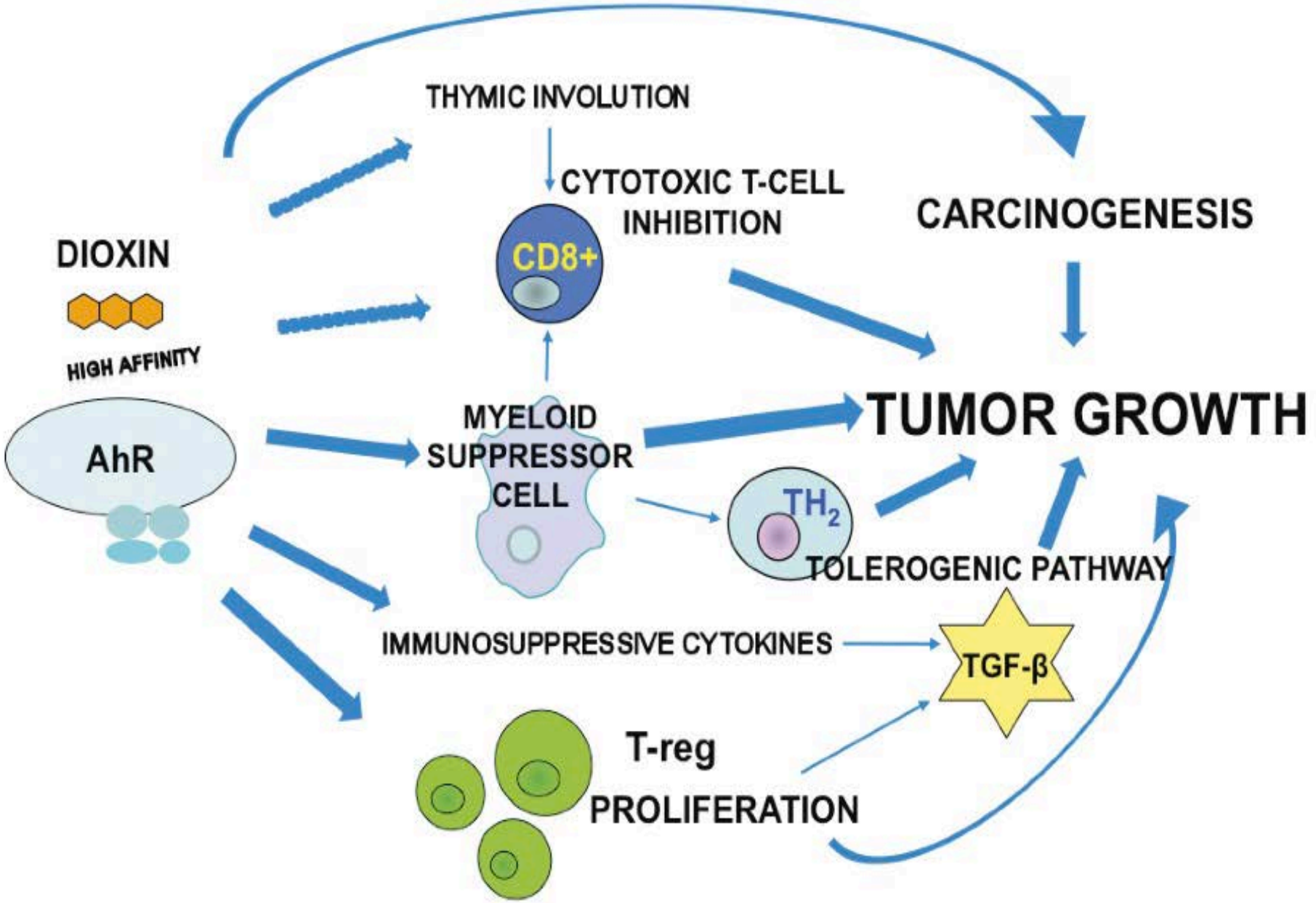
PCB MAIN EXPERIMENTAL TOXICITY MECHANISMS

ARNT, aryl hydrocarbon receptor nuclear translocator

XRE, xenobiotic-response regulator

CYT P 4501A1 , enzymatic lines activator


Environmental Ligands: PCDHs, PCBs, Dioxins, and Furans
Recombinant Cell
AhR Complex
Translocation
ARNT
DRE
CYP1A1 or other genes
Nucleus of the cell
DRE
Luciferase
Translation
mRNA
New Polypeptides
Increased Cytochrome P-4501A1 and Other Proteins
Luciferase Activity
DRE = Dioxin Responsive Element
= Dioxin-like compounds: PCDHs, PCBs, Dioxins and Furans
ARNT = AhR Nuclear Translocator protein
AhR Complex = Aryl hydrocarbon Receptor Complex
Induction of light is directly proportional to concentration of dioxin TEQ in the sample.


THYMIC INVOLUTION
CYTOTOXIC T-CELL INHIBITION
CARCINOGENESIS
DIOXIN
CD8+
HIGH AFFINITY
AhR
MYELOID SUPPRESSOR CELL
TUMOR GROWTH
TH2
TOLEROGENIC PATHWAY
IMMUNOSUPPRESSIVE CYTOKINES
TGF-β
T-reg
PROLIFERATION

PCBs (their metabolites) main toxicity mechanisms

- **Interaction with receptors as *aryl hydro-carbon complex; androstane, pregnane receptors* (controlling xenobiotics effect as steroids/ hormones**
- **Oxidative stress (reactive intermediates or interference in repair their damage).**
- **Modulation of *cell signaling , adhesion, migration, tumor promotion***

Genes and pathways involved in melanoma mechanisms

CDKN2A gene

p16CDKN2A-CDK4-RB e p14CDKN2A-MDM2-p53 pathway

NRAS-BRAF gene

MAPK e PI3K-AKT pathway

cKIT gene

MITF gene.

Gene CDKN2A

Oncosoppressore ed agisce con un meccanismo d'azione di tipo recessivo.

In particolare, mutazioni di questo gene sono 7-10 volte più frequenti nei pazienti con una forte storia di ricorrenza familiare di melanoma

Geni NRAS-BRAF

RAS e BRAF giocano un ruolo centrale nella regolazione della crescita, sopravvivenza e proliferazione cellulare.

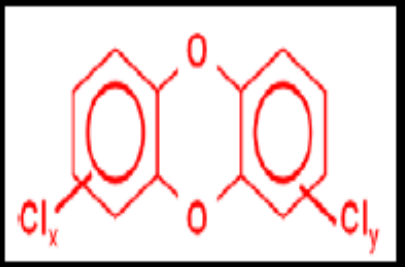
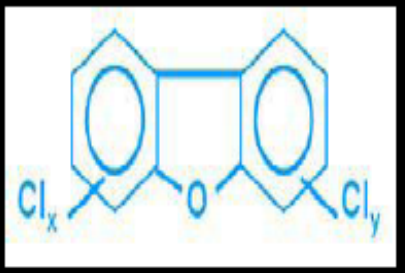
I melanomi che insorgono in aree cutanee esposte in maniera intermittente al sole e che, quindi, non rappresentano i segni di un danno solare cronico, presentano la più alta frequenza di mutazioni del gene BRAF

Diverse pathway per stesso gene (BRAF)

Evidenziata una maggiore incidenza di mutazioni BRAF nei melanomi a crescita verticale rispetto a quelli a crescita superficiale, nonché l'osservazione di amplificazioni delle regioni genomiche 9p21 e 1p22 in maniera prevalente nei melanomi nodulari

Meccanismi alternativi a quelli di progressione «lineare»

Coinvolgimento di cellule staminali tessutali, le cui alterazioni darebbero direttamente origine a cellule di melanoma in fase di crescita superficiale oppure verticale ovvero, addirittura, in fase metastatica

Nome	Struttura	Congeneri	Congeneri tossici
PCDDs		75	7
PCDFs		135	10
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Toxic equivalency (TEF;TEQ)

The Toxicity Equivalency Factor (**TEF**)expresses the toxicity of dioxins, furans and PCBs in terms of the most toxic form of dioxin, 2,3,7,8-TCDD. The toxicity of the individual congeners may vary by orders of magnitude.

With the TEFs, the toxicity of a mixture of dioxins and dioxin-like compounds can be expressed in a single number - the **Toxic equivalency** (**TEQ**).

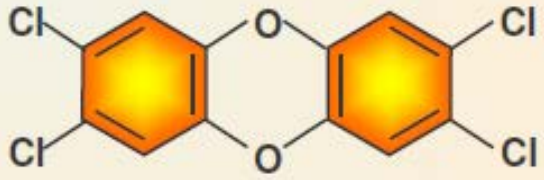
Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/2002

IL CONCETTO DELL'EQUIVALENZA DI TOSSICITÀ (I)
(TEQ, *toxicity equivalent*)

$$\text{Total TEQ} = \Sigma\, C_{congener} \times TEF_{congener}$$

=

Equivalenza di tossicità con



2,3,7,8-Tetraclorodibenzodiossina

TEF = fattore di tossicità equivalente

Toxic equivalency (TEF;TEQ)

The TEF/TEQ concept has been developed to facilitate risk assessment and regulatory control.

It can theoretically be applied to any group of chemicals satisfying the extensive similarity criteria used with dioxins, **primarily that the main mechanism of action is shared across the group**. Thus far, only the DLCs have had such a high degree of **evidence of toxicological similarity**

Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/2002

The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds.

Van den Berg et al .

Toxicol Sci. 2006 Oct;93(2):223-41. Epub 2006 Jul 7.

	I-TEF	WHO-TEF
2,3,7,8-TCDD	1,0	1,0
1,2,3,7,8-PeCDD	0,5	1,0
1,2,3,4,7,8-HxCDD	0,1	0,1
1,2,3,6,7,8-HxCDD	0,1	0,1
1,2,3,7,8,9-HxCDD	0,1	0,1
1,2,3,4,6,7,8-HpCDD	0,01	0,01
OCDD	0,001	0,0001
2,3,7,8-TCDF	0,1	0,1
1,2,3,7,8-PeCDF	0,05	0,05
2,3,4,7,8-PeCDF	0,5	0,5
1,2,3,4,7,8-HxCDF	0,1	0,1
1,2,3,6,7,8-HxCDF	0,1	0,1
2,3,4,6,7,8-HxCDF	0,1	0,1
1,2,3,7,8,9-HxCDF	0,1	0,1
1,2,3,4,6,7,8-HpCDF	0,01	0,01
1,2,3,4,7,8,9-HpCDF	0,01	0,01
OCDF	0,001	0,0001
3,4,4',5 tetracloro bifenile (PCB 81)	-	0,00010
3,3',4,4' tetracloro bifenile (PCB 77)	-	0,00010
2',3,4,4',5 pentacloro bifenile (PCB 123)	-	0,00010
2,3',4,4',5 pentacloro bifenile (PCB 118)	-	0,00010
2,3,4,4',5 pentacloro bifenile (PCB 114)	-	0,00050
2,3,3',4,4' pentacloro bifenile (PCB 105)	-	0,00010
3,3',4,4',5 pentacloro bifenile (PCB 126)	-	0,1
2,3',4,4',5,5' esacloro bifenile (PCB 167)	-	0,00001
2,3,3',4,4',5 esacloro bifenile (PCB 156)	-	0,00050
2,3,3',4,4',5' esacloro bifenile (PCB 157)	-	0,00050
3,3',4,4',5,5' esacloro bifenile (PCB 169)	-	0,01
2,3,3',4,4',5,5' eptacloro bifenile (PCB 189)	-	0,00010

REGOLAMENTO (UE) N. 277/2012 DELLA COMMISSIONE del 28 marzo 2012

(modifica degli allegati I e II della direttiva 2002/32/CE)

(3) **Ciascuno dei congeneri** di diossine o di PCB diossina- simili che hanno una rilevanza tossicologica **presenta un diverso livello di tossicità**. Per poter sommare la tossicità di questi diversi congeneri è **stato introdotto il concetto di fattori di tossicità equivalente (*toxic equivalency factors* — TEF)** per agevolare la valutazione del rischio e il controllo normativo

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 107 (2016)

Polychlorinated Biphenyls and Polybrominated Biphenyls

PCBs are *carcinogenic to humans (Group 1)*. "Dioxin-like" PCBs, with a toxicity equivalency factor (TEF) according to WHO (PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-169, PCB-156, PCB-157, PCB-167, PCB-189), are *carcinogenic to humans (Group 1)*.

However, the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs.

IARC Monograph Vol. 107**, 2016**

The classification is based on consistent association between PCB exposure and **increased risk of melanoma in humans.**

There is also limited evidence from some studies suggesting that exposure is linked to increased risks of non-Hodgkin lymphoma and breast cancer.

IARC Monograph Vol. 107**, 2016**

PCBs and their metabolites have multiple modes of action.

Highly chlorinated congeners are very persistent and interact with various receptors

Less chlorinated congeners involved in oxidative metabolism may produce oxidative stress and genotoxicity

IARC 2016

EPIGENETICA

Le informazioni contenute nel DNA vengono continuamente influenzate da meccanismi biochimici che comprendono metilazione, microRNA e assetto istonico, che continuamente si modellano e si adattano a seconda dei segnali - fisici, chimici, biologici - con cui entra in contatto.

Bertazzi et al 2013

Exposure to persistent organic pollutants and sperm DNA methylation changes in Arctic and European populations.

Persistent organic pollutants (POPs), such as PCBs (polychlorinated biphenyls) and DDT [1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane], are environmental contaminants with potential endocrine disrupting activity. DNA methylation levels in peripheral blood lymphocytes have been associated with serum concentrations of POPs in Greenland Inuit and Korean populations.

POP exposure appears to have a limited negative impact on sperm DNA methylation levels in adult males

Consales C, Toft G, Leter G, Bonde JP, Uccelli R, Pacchierotti F, Eleuteri P, Jönsson BA, Giwercman A, Pedersen HS, Struciński P, Góralczyk K, Zviezdai V, Spanò M
.Environ Mol Mutagen. 2016 Apr;57(3):200-9. doi: 10.1002/em.21994.

Exposure to coplanar PCBs induces endothelial cell inflammation through epigenetic regulation of NF-κB subunit p65.

Epigenetic modifications of DNA and histones alter cellular phenotypes without changing genetic codes and may contribute to associated disease risks. Here we test the hypothesis that endothelial cell dysfunction induced by exposure to polychlorinated biphenyls (PCBs) is mediated in part though histone modifications**.**

In this study, human vascular endothelial cells were exposed to physiologically relevant concentrations of several PCBs congeners (e.g., PCBs 77, 118, 126 and 153) followed by quantification of inflammatory gene expression and changes of histone methylation

Liu D, Perkins JT, Petriello MC, Hennig B.Toxicol Appl Pharmacol. 2015 Dec 15;289(3):457-65. doi: 10.1016/j.taap.2015.10.015.

EPIGENETICA PCB MELANOMA

PUB MED

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