

Existe una diversidad de mecanismos por los que los COPs pueden perjudicar la salud humana.

**Existe una
diversidad de mecanismos:**

**no sólo
la disrupción endocrina.**

- DDT and some PCBs have weak estrogenic and anti-androgenic effects, while other OCs have antiestrogenic activity.
- But long half-lives in human body and high concentrations in target tissues.

- Some congeners such as PCB 138 can bind to estrogen receptors and modulate the expression of oncogenes, including *ras* genes.
- PCB mixtures may increase *c-raf* and *c-erb* mRNA levels in human liver cells, i.e., act as tumor promoters through activation of cell proliferation pathways.
 - Gribaldo L et al. *J Tox Env Health* 1998.

Even if role as “tumor promoters” remains more widely accepted...

- **Some estrogen metabolites (e.g., 16 α -OH estradiol) can be complete carcinogens (able to covalently bind to DNA, cause the initiating mutations).**
- **Hormonal effects may complete the development of tumors.**
 - Roy & Liehr. *Mutat Res* 1999.
 - Service RF. *Science* 1998.
 - Yager & Liehr *Annu Rev Pharmacol Toxicol* 1996.

- **Free radicals and oxidative DNA damage are produced during oxidation of lower chlorinated PCBs.**
 - Cogliano VJ. *Env Health Perspect* 1998.
 - Oakley JJ et al. *Chem Res Toxicol* 1996.

- Even relatively low doses of DDT induce CYP450. The result is altered metabolism of many drugs, xenobiotics, steroid hormones.
- Exposure to OCs can be a potential effect modifier of other exposures.

PCBs are **broad-acting** toxicants occurring in **complex mixtures** and accurate risk assessment has been elusive. **Focusing on** the **most potent** congeners -aryl hydrocarbon receptor (**AhR**) **agonists**- has made it impossible to confirm or deny significant contributions from the **more prevalent** components of the mixtures.

Hansen LG. Stepping backward to improve assessment of PCB congener toxicities. Environ Health Perspect 1998; 106 (Supl 1): 171-189.

Responses not mediated through the AhR are presented and emphasize large data gaps. AhR-focused objectives unintentionally created the wrong impression that nonplanar PCBs have little potential for hazards to humans and wildlife.

Hansen LG. Stepping backward to improve assessment of PCB congener toxicities. Environ Health Perspect 1998; 106 (Supl 1): 171-189.

Pulses of exposure to more labile mixtures may contribute to developmental effects without leaving a residue record.

Hansen LG. Stepping backward to improve assessment of PCB congener toxicities. Environ Health Perspect 1998; 106 (Supl 1): 171-189.

A comprehensive list of PCB congeners is proposed that would provide more adequate data upon which to base associations with adverse outcomes.

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“ results were inconsistent... ”

Atención: efectos indirectos

- **Inducción enzimática:
procarcinógeno → carcinógeno.**
- **Alteraciones reparación DNA.**
- **Alteraciones apoptosis.**
- **Proporcionar ventaja crecimiento.**
- **Alteraciones inmunológicas.**
- **.....**

“ results were inconsistent... ”

Atención: efectos indirectos

Atención: interacciones.

SÍ: difíciles de detectar:

efectos sutiles, a largo plazo.

NO negligibles:

↑↑↑ N° personas expuestas.

**Los COPs
pueden causar una
diversidad de efectos
sobre la salud humana / 2:
Atención a los resultados
de los estudios
epidemiológicos.**

**Journal of the National Cancer Institute 2001.
DDE and PCBs and Breast Cancer: Combined
Analysis of Five U.S. Studies. Francine Laden et al.**

**1,400 women with breast cancer and 1,642
control women [mainly from northeast U.S.].
Maximizes statistical power to detect effect
modification by other breast cancer risk
factors.**

**OR for breast cancer associated with
PCBs: 0.94 (95% CI = 0.73 to 1.21)
DDE: 0.99 (95% CI = 0.77 to 1.27).**

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