Combined effects of carcinogens

Institute of Environmental Medicine

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The Lifetime Probability of Developing Cancer for Women, 2005-2007*

Site	Risk
All sites†	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 16
Colon & rectum	1 in 20

The Lifetime Probability of Developing Cancer for Men, 2005-2007*

Site	Risk
All sites†	1 in 2
Prostate	1 in 6
Lung and bronchus	1 in 13
Colon and rectum	1 in 19

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.5.0 Statistical Research and Applications Branch, NCI, 2010. http://srab.cancer.gov/devcan

National Cancer Institute

477 chemicals tested in NTP cancer test analyzed

278 rat carcinogens

197 (71%) gave sex difference in at least one non-reproduktive organ

68 induced tumors in males only

19 induced tumors in females only

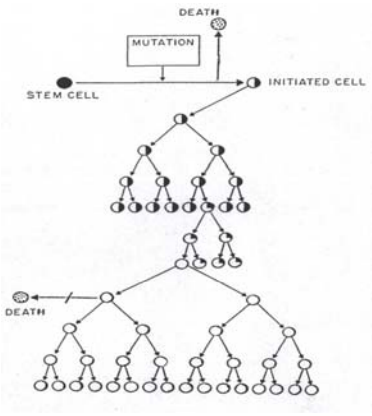
Overall 1.69 ($p<0.001$) more tumors in male rats

Kadekar S et al, Toxicol Pathol, in press.

Interaction between carcinogens and hormones?

Cancerbiology

- Mutation
- Growth advantage
- Clonal expansion
- Accumulation of mutations
- Heterogenicity, mutated genes in different combinations
- 286 tumor suppressor genes
- 91 oncogenes



Initiation-promotion

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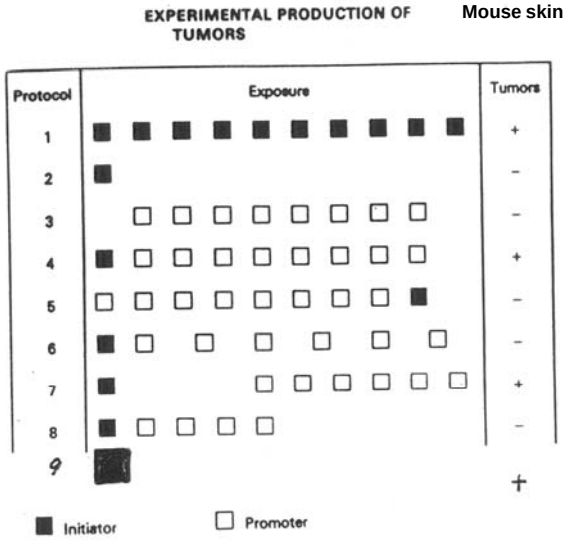
Mouse skin model



Genotoxic Non-Genotoxic

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Synergistic carcinogenic effects
human studies

Asbestos and smoking

-asbestos – 5 fold increased risk for lung cancer
-smoking – 10 fold increased risk
-combined exposure – 50 fold increased risk

Selikoff et al 1968

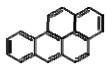
- Induce similar types of mutation
- Asbestos may enhance the mutagenic effect of tobacco smoke

Toxic equivalency factors (TEFs) in risk assessment of Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs)

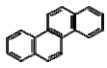
Mutagenic, carcinogenic, tumor promoters

- result from incomplete combustion of organic matter and are emitted from many sources (tobacco smoke, diesel exhaust, aluminium production…)



Benzo[a]pyrene

Phenanthrene



Chrysene

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International Agency for Research on Cancer (IARC) classification of PAH containing mixtures and exposures

Group 1- human carcinogens
BaP, Coal tar,
Aluminium production, coke production, tobacco smoke

Group 2A Probably carcinogenic to humans
DBalP

Group 2B Possibly carcinogenic to humans
4 different PAHs

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Risk assessment of PAH mixtures

TEFs for individual PAH (relative to BaP) =BaP equivalent dose

RESPONSE ADDITION= assuming additivity of their carcinogenic effect

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TEF-concept

- Well characterized reference compound
- Similar toxic effects for all members
- TEFs for different endpoints are similar
- Effects in a mixture are additive

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TEF-values for PAHs

Oral carcinogenic data only for B(a)P

TEF values for different PAHs from different endpoints such as; skin application, ip injections, s.c. Application

PAH-DNA adducts in vitro tests

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Comparison between different TEF-values

Boström et al EHP, 2002

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Table 13. Relative potency of individual PAHs compared with B[*a*]P (TEF values), according to different authors.[a]

Compound	Chu and Chen (1984) (cit. Nisbet and LaGoy 1992)	Clement (1986) (cit. Nisbet and LaGoy 1992); Krewski et al. (1989)	Nisbet and LaGoy (1992)	The Netherlands (RIVM 1989)	CARB (1994); Collins et al. (1998)	Health Canada (Meek et al. 1994)	Ontario (Muller 1997)	Larsen and Larsen (1998)
Anthracene			0.01	0				0.0005
Phenanthrene			0.001	0.01			0.00064	0.0005
Benz[*a*]anthracene	0.013	0.145	0.1	0–0.04	0.1		0.014	0.005
Benzo[*c*]phenanthrene							0.023	0.023
Chrysene	0.001	0.0044	0.01	0.05–0.89	0.01		0.026	0.03
Fluoranthene			0.001	0–0.06				0.05
Pyrene		0.081	0.001				0	0.001
B[*a*]P	1	1	1	1	1	1	1	1
Benzo[*e*]pyrene		0.004					0	0.002
Benzo[*b*]fluoranthene	0.08	0.14	0.1		0.1	0.06	0.11	0.1
Benzo[*j*]fluoranthene		0.061			0.1	0.05	0.045	0.05
Benzo[*k*]fluoranthene	0.04	0.066	0.1	0.03–0.09	0.1	0.04	0.037	0.05
Cyclopenta[*cd*]pyrene		0.023					0.012	0.02
Dibenzo[*a,h*]anthracene	0.69	1.11	5				0.89	1.1
Anthanthrene		0.32					0.28	0.3
Benzo[*ghi*]perylene		0.022	0.01	0.01–0.03			0.012	0.02
Dibenzo[*a,e*]pyrene					1		1.0[b]	0.2
Dibenzo[*a,h*]pyrene					10		1.2	1
Dibenzo[*a,i*]pyrene					10			0.1
Dibenzo[*a,l*]pyrene					10		100[b]	1
Indeno[1,2,3-*cd*]pyrene	0.017	0.232	0.1	0–0.08	0.1	0.12	0.067	0.1

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TEF-values applied for PAH mixtures underestimate the risk

- Larsen, Larsen TEF-values applied for PAH mixtures *Schneider et al , J Appl Toxicol 2002*
- **Coal tar – the potency predicted to 1.5 times in the reality 10 times**

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Problems

Oxy- and nitro PAHs not included in TEF scales

Tumorpromoting PAHs lack TEF-values

Mixtures induce tumors in other organs than BaP

Different PAHs induce tumors by different mechanisms

Effect of soil samples on DNA-damage signaling

Experimental model

Cells exposed to PAH fractions of soil extracts corresponding to:

1 mg soil

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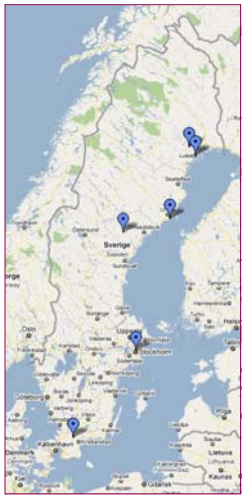
Soil samples

Complex PAH mixtures extracted from contaminated soil.

6 different industrial areas of Sweden:

- Wood preservation sites (**Boden**, **Hässleholm**, **Forsmo**, **Holmsund**)
- Gas work site (**Husarviken**)
- Coke oven site (**Luleå**)



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PAH analysis

PAHs (ug/g soil)	Luleå	Holmsund	Husarviken	Forsmo	Hässleholm
Naphthalene	7.1	2.7	12	0.54	0.64
Acenaphthylene	2.9	2.2	28	1.3	3.8
Acenaphthene	10	28	2.8	11	38
Flourene	17	20	38	26	26
Phenanthrene	71	29	410	12	5
Anthracene	12	38	74	53	48
Flouranthene	57	665	530	697	563
Pyrene	37	391	370	536	298
Benz[a]anthracene	24	96	240	125	130
Chrysene	26	113	230	135	139
Benzo[k]fluoranthene	11	21	110	30	29
Benzo[a]pyrene	18	16	160	37	39
Dibenz[a,h]anthracene	3.8	2.4	44	4.4	4.2
Indeno[cd]pyrene	15	7.9	140	15	15
Benzo[ghi]perylene	13	5.7	120	12	11
1-Indanone	0.11	0.38	0.46	0.65	0.45
9-Flourenone	48	16	83	6.5	5.3
Anthracene-9,10-dione	6.4	15	51	15	3.8
4H-Cyclopenta[def]phenanth	5.3	134	78	139	75
2-Methylanthracene-dione	0.75	4.9	6.8	9.9	1.7
Benzoflourenone	10	21	84	28	18
7H-Benz[de]anthracene-7-one	2.8	4.1	22	0.95	1.7
Benz[a]anthracene-7,12-dione	0.71	7.6	6.3	9	4.7
Naphthacene-5,12-dione	0.41	17	9.5	29	11
Benzo[cd]pyrenone	8.8	22	67	26	21

Effects on DNA damage signaling

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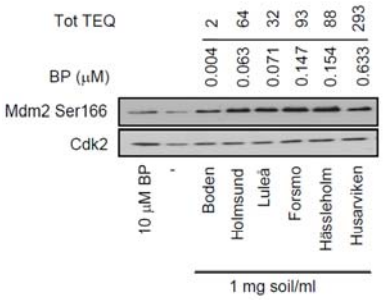
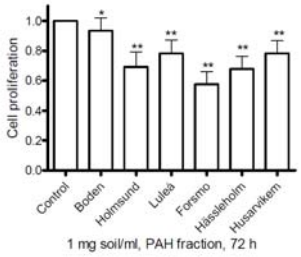
Effects on p53 signaling





No correlation to TEQ values

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Prolonged activation of DNA-damage signaling

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Complex PAH mixture from soil extracts

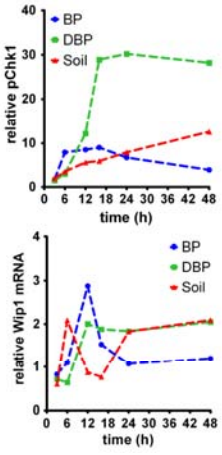
↓

Persistent DNA damage

↓

↗ phospho-Chk1

↗ Wip1 mRNA



Niziolek-Kierecka M, Dreij K, et al.
Chem ResToxicol, in press.

Summary

TEF-concept is not sufficient for risk assessment of PAHs

- Do mixtures affect DNA-repair?

Identify PAHs which induce synergistic effects

- Mixture Assessment Factors

- Mode of action-based risk assessment

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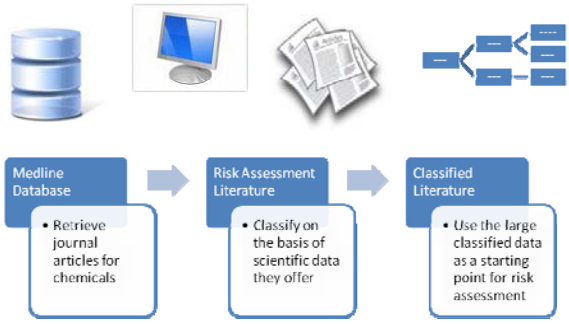
Text Mining for Cancer Risk Assessment

Collaboration with the University of Cambridge Computer Laboratory

Natural Language and Information Processing Group

The Ultimate Goal of Natural Language Processing
To get computers to deal with language the way humans do

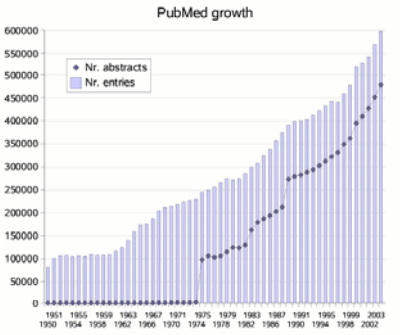
GRAB literature classifier



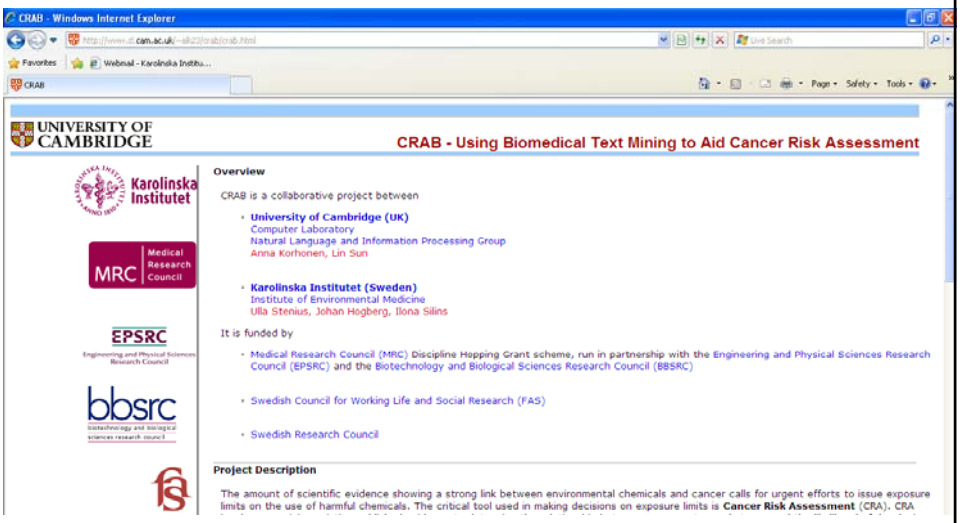
support cancer risk assessment

2005: 13 miljon references

Today over 18 miljon references, 2000-4000 added each day



http://www.cl.cam.ac.uk/~alk23/crab/crab.html



Mode of action (MOA)

- Descibes the key events resulting in cancer development
- Aflatoxin B1; adduct → mutation → cancer

Most commonly used MOAs are genotoxic and nongenotoxic

MOA analysis for the mixture or exposure

Critical Reviews in Toxicology, 39:97–138, 2009

ISSN: 1040-8444 print / 1547-6898 online
DOI: 10.1080/10408440802307467

A Preliminary Operational Classification System for Nonmutagenic Modes of Action for Carcinogenesis

D. Hattis
George Perkins Marsh Institute, Clark University, Worcester, Massachusetts

M. Chu
National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC, USA

N. Rahmioglu, R. Goble, P. Verma, K. Hartman, and M. Kozlak
George Perkins Marsh Institute, Clark University, Worcester, Massachusetts

This article proposes a system of categories for nonmutagenic modes of action for carcinogenesis. The classification is of modes of action rather than individual carcinogens, because the same compound can affect carcinogenesis in more than one way. Basically, we categorize modes of action as: (1) co-initiation (facilitating the original mutagenic changes in stem and progenitor cells that start the cancer process) (e.g. induction of activating enzymes for other carcinogens); (2) promotion (enhancing the relative growth vs differentiation/death of initiated clones (e.g. inhi-

Taxonomy classifying literature evidence for carcinogenic mode of action

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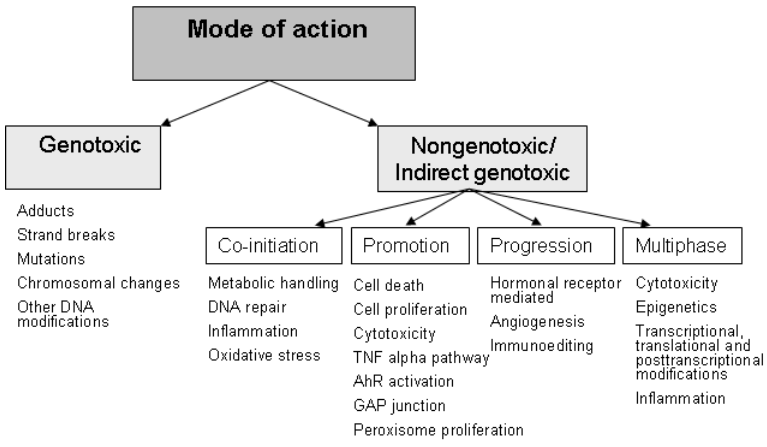

Hattis et al 2009

Analysis of the published literature for identification of carcinogenic mode of action


BMC Bioinformatics

BioMed Central

Research article

Open Access

The first step in the development of text mining technology for cancer risk assessment: identifying and organizing scientific evidence in risk assessment literature

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Email: Anna Korhonen* - alk23@cl.cam.ac.uk; Ilona Silins - Ilona.Silins@ki.se; Lin Sun - Lin.Sun@cl.cam.ac.uk; Ulla Stenius - ulla.stenius@ki.se

* Corresponding author

CRAB- a text mining tool for literature review and knowledge discovery in cancer risk assessment and research

Korhonen A et al 2012, PLoS ONE, in press

Data and literature gathering in chemical cancer risk assessment.

Silins I et al Integr Environ Assess Manag. 2012 Jan 3. doi: 10.1002/ieam.1278.

27 000 PubMed abstracts for Cadmium classified by CRAB

- Mode of Action 6164
  - genotoxic 646
    - strand breaks 107
    - adducts 12
    - chromosomal changes 181
      - micronucleus 85
      - chromosomal aberrations 52
    - mutations 170
    - other dna mods 154
  - nongenotoxic/indirect genotoxic 4656
    - co-initiation 1570
      - DNA repair 96
      - metabolic handling
      - oxidative stress 1028
      - inflammation 36
    - promotion 1670
      - cell proliferation 328
      - cell death 489
      - peroxisome proliferation 4
      - cytoxicity 234
      - GAP junction
      - AhR activation 7
      - TNF alpha pathway activation 22
    - progression 281
      - hormonal receptor-mediated mechanism 47
      - immunosuppression 153
      - angiogenesis

Cadmium/epidemiological studies/tumors

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- X irrelevant negative remove tags

Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers.

BACKGROUND: Laboratory workers have long been suspected of having increased risks of cancer due to their occupation. We evaluated laboratory workers. MATERIALS AND METHODS: The cohort was comprised of 4,722 laboratory workers reported to the Finnish Regi standardized incidence ratios (SIR) for cancers and their 95% confidence intervals (CI) were calculated based on data of the Finnish Cancer workers were potentially exposed, were chromium (VI), carbon tetrachloride, cadmium, benzene, and chloroform. From this cohort, 174 pe for cancer of all sites combined was 0.99 (CI 0.85-1.14). None of the cancer-specific SIRs were significantly elevated. Slight excesses were expected) and leukemia (four observed, three expected). CONCLUSIONS: This study did not suggest any major cancer risks among Finnis short (on an average 15.7 years) to reveal possible cancer risks requiring a longer induction period.

More info

- X irrelevant negative remove tags

Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000.

AIMS: To investigate mortality from lung cancer in nickel-cadmium battery workers in relation to cumulative exposure to cadmium hydroxide factory engaged in the manufacture of nickel-cadmium batteries in the West Midlands of England was investigated for the period 1947-2000 and employed for a minimum period of 12 months. Work histories were available for the period 1947-86; the factory closed down in 1992. Poisson regression. RESULTS: Based on serial mortality rates for the general population of England and Wales, significantly increased morta expected (Exp) 0.7, standardised mortality ratio (SMR) 559, p<0.05), non-malignant diseases of the respiratory system (Obs 61, Exp 43.0, system (Obs 10, Exp 4.1, SMR 243, p<0.05). Non-significantly increased SMRs were shown for lung cancer (Obs 45, Exp 40.7, SMR 11 Estimated cumulative cadmium exposures were not related to risks of lung cancer or risks of chronic obstructive pulmonary diseases, even w CONCLUSIONS: The study findings do not support the hypotheses that cadmium compounds are human lung carcinogens.

More info

- X irrelevant negative remove tags

Urinary cadmium and mortality among inhabitants of a cadmium-polluted area in Japan.

Literature distribution for genotoxic/ non-genotoxic chemicals

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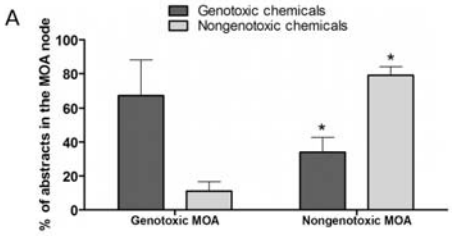
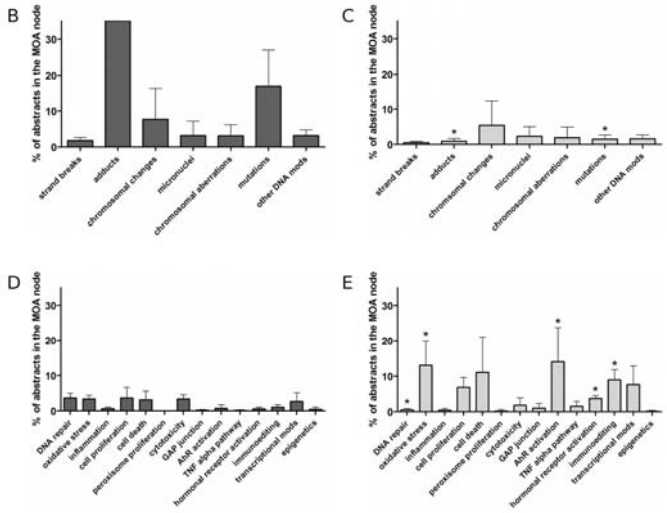


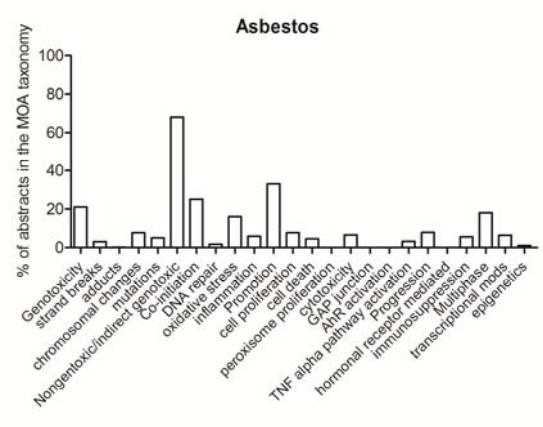
Genotoxic: 1,3-butadiene, 4-aminobiphenyl, dibenzo(al)pyrene, ethylene oxide
Non-genotoxic: TCDD, PCB126, PCB153, pentachlorodibenzofuran

Literature distribution for genotoxic/ non-genotoxic chemicals

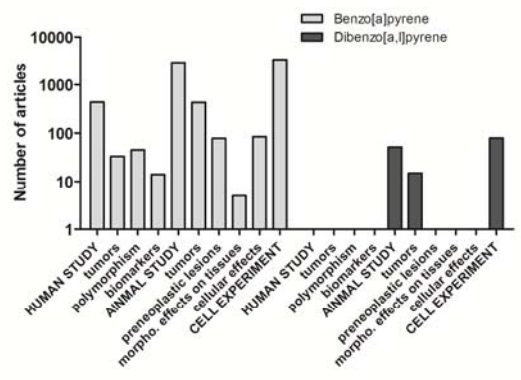


CRAB profile for asbestos

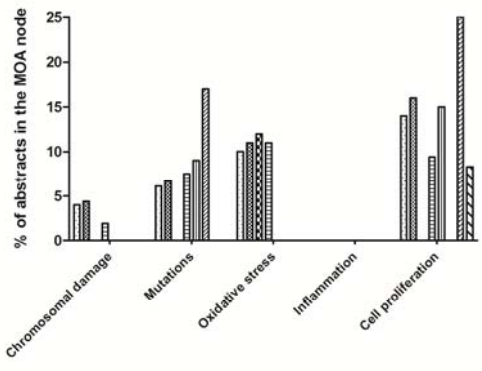
1300 of 10970 abstracts relevant for MOA



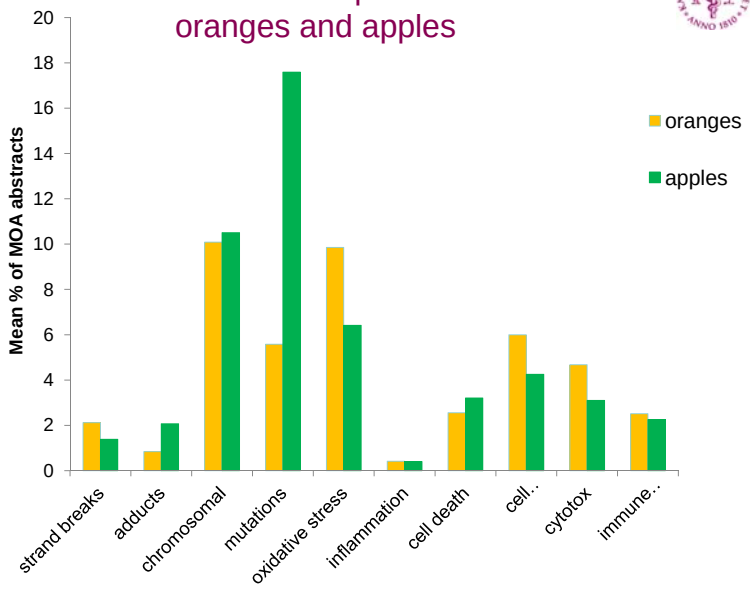
Identification of data gaps



Distribution of classified literature for 9 antifungar pesticides (Triazoles)



Literature distribution of pesticides found in oranges and apples



Environmental cancer risks?

Cancer caused by chemicals grossly underestimated.

80 000 chemicals – un- or understudied and largely unregulated, exposure to potential environmental carcinogens is widespread

Presidents Cancer Panel 2009, National Cancer Institute