# THE CANCER REVOLUTION

## Additional Material for Chapter 11

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### Environmental chemicals and cancer

Government agencies have taken it upon themselves to evaluate data on single chemicals for their ability to induce cancers (carcinogens), mutations (mutagens) and birth defects (teratogens) for decades. The International Agency for Research on Cancer (IARC)[1], for example, was established as an intergovernmental agency of the World Health Organization (WHO) of the United Nations (UN) in 1965 in order to create a central repository of chemical agents that have been demonstrated to cause, or are suspected of causing, cancer. The classification system used by the IARC is based on the scientific consensus among the expert members of the relevant scientific review panel at the IARC. It is worth noting that the IARC has had a long history of criticism from independent quarters for making 'soft-touch' decisions that avoid negative impacts on the chemical or tobacco industry (Ferber, 2003).

**Table 1. International Agency for Research on Cancer categorisation of carcinogens and examples***

| IARC category | Scientific basis of IARC classification | No. of entries (2012) | Examples (as of 2012) |
|---|---|---|---|
| Group 1 | Carcinogenic to humans | 109 | Alcoholic beverages, aflatoxins, arsenic, asbestos, benzene, benzopyrene, coal, coat tar, diesel exhaust, dioxin, Epstein-Barr virus, postmenopausal oestrogen or combined progesterone-oestrogen therapy, oestrogen/progesterone contraceptives, ethylene oxide, formaldehyde, Helicobacter pylori infection, Hepatitis B and C virus (chronic infection), human papilloma virus (HPV) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, ionizing radiation, leather dust, untreated mineral oils, naphthylamine, nickel compounds, paints (occupational exposure of painters), radionuclides, various forms of radium and their decay products, rubber manufacturing industry, salted fish (Chinese style), shale oils, crystalline silica dust, solar radiation, soot, Tamoxifen, tobacco (smoking, second-hand smoke, smokeless, chewing), vinyl chloride, wood dust, X- and Gamma-radiation |

| IARC category | Scientific basis of IARC classification | No. of entries (2012) | Examples (as of 2012) |
|---|---|---|---|
| Group 2A | Probably carcinogenic to humans | 65 | Acrylamide, anabolic steroids, adriamycin, wood (and other biomass) fuels, bitumens, Captafol, chlorinated toluenes, chlorozotocin, Cisplatin, creosotes, cyclopentalpyrene, dibenzacridine, dibenzopyrene, dimethylhydrazene, dimethyl sulphate, ethyl carbamate (urethane), ethylene dibromide, emissions from high temperature frying, occupational exposure as hairdresser or barber, inorganic lead compounds, infection by Plasmodium falciparum (that causes malaria), mate (hot), Merkel cell polyomavirus, 5-methoxypsoralen, methyl methanesulfonate, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ingested nitrates or nitrites (under conditions that result in endogenous nitrosation), nitrogen mustard, 1-nytropyrene, N-nitrosodimethylamine, N-nitrodimethylamine, 2-nitrotoluene, application of non-arsincal insecticides (occupational exposure), petroleum refining, polychlorinated biphenyls (PCBs), shift work involving disruption of circadian rhythms, styrene-7-8-ocxide, tetrachloroethylene (perchloroethylene), 1,2,3-trichloropropane, vinyl bromide, vinyl fluoride |
| Group 2B | Possibly carcinogenic to humans | 275 | Aflatoxin M1, acetaldehyde, acetamide, para-aminoazobenzene, anthraquinone, benzofuran, benzophenone, benzyl violet 4B, bitumens, occupational exposure to straight-run bitumens and their emissions during road paving, caffeic acid, carbon black, carbon tetrachloride, chloroform, cobalt and cobalt compounds, cobalt metal without tungsten carbide, coconut oil diethanolamine condensate, para-dichlorobenzene, diethanolamine, ethylbenzene, gasoline, human immunodeficiency virus type 2 (infection with), human papillomavirus types 26, 53, 66, 67, 70, 73, 82, lead, magnetic fields (extremely low-frequency), methylmercury compounds, metronidazole, mitoxantrone, naphthalene, nickel (metallic and alloys), nitrobenzene, ochratoxin A, pickled vegetables (traditional in Asia), phenobarbital, styrene, talc-based body powder (perineal use of) |

| IARC category | Scientific basis of IARC classification | No. of entries (2012) | Examples (as of 2012) |
|---|---|---|---|
| Group 3 | Not classifiable as to carcinogenicity in humans | 503 | Aciclovir, actinomycin D, amaranth, para-aminobenzoic acid, ampicillin, anaesthetics (volatile), arsenobetaine and other organic arsenic compounds that are not metabolized in humans, atrazine, benzoyl peroxide, bisphenol A diglycidyl ether (Araldite), bisulfites, caffeine, carrageenan (native), chlorinated drinking water, chloroquine, cholesterol, chromium (metallic), coal dust, coumarin, crude oil, cyclamates (sodium cyclamate), diazepam, electric fields (extremely low-frequency), electric fields (static), ethylene, fluorides (inorganic, used in drinking-water), haematite, human papillomavirus genus beta (except types 5 and 8) and genus gamma, lead compounds, organic (NB: Organic lead compounds are metabolized at least in part, to ionic lead both in humans and animals. To the extent that ionic lead, generated from organic lead, is present in the body, it will be expected to exert the toxicities associated with inorganic lead), magnetic fields (static), mineral oils (highly refined), paracetamol (acetaminophen), polyethylene, polypropylene, polystyrene, saccharin and its salts, tea, temazepam, vitamin K substances. |
| Group 4 | Probably not carcinogenic to humans | 1 | Caprolactam. |

* See http://monographs.iarc.fr/ENG/Classification/index.php for full listing of carcinogens by group, cancer site, chemical identification (CAS) number or alphabetical order.

Important observations that can be made from surveying the IARC's list are that with just 449 agents (mainly chemicals, but also some occupational exposures) listed in the Group 1, 2A and 2B categories, there are a surprisingly large number of industrial chemicals for which no carcinogenic risk has been identified. We must ask: Does this make the roughly 19,500 industrial chemicals in common usage safe and in no way implicated in cancer? It would be a brave—or foolish— person to claim this. The reality is that proving or even suspecting the role of a chemical agent in the development of cancer is a highly complex process (see below).

Added to this, is the premise that government agencies, like the IARC, have limited resources and their views may be compromised owing to evidence of 'revolving doors' between corporations and agency personnel or scientific experts that contribute to opinions. Sir Richard Doll, often regarded as the most prominent epidemiologist (the a branch of medical science that deals with the incidence, distribution and control of disease in a population) of the 20th century, was himself posthumously accused of being influenced by corporations to their benefit. After his death in 2005, it was revealed that Monsanto, Dow, ICI and others, made large and, at the time, undisclosed consultancy payments to him during the time he was evaluating their products. [2]

**Challenges in proving carcinogenicity**

There are a number of reasons why, relatively speaking, so few chemicals to which we are exposed have been identified as proven carcinogens. These include:

1. Only a few chemicals, such as those on the IARC's Group 1, and probably Group 2A, and possibly also the Group 2B list, are carcinogenic. This is highly unlikely given that only around 5-10% of cancers are thought to be linked to inherited, genetic factors.[3] This means that that 90-95% of cancers are linked to environmental causes and behaviour. Among the environmental causes are natural as well as synthetically produced chemicals. Increasing amounts of research is demonstrating the importance of behavioural and lifestyle choices that we know contribute to increased cancer risk, e.g., physical inactivity, heavy alcohol consumption, excessive exposure to the sun (Buck and Frosini, 2012; Ezzati and Riboli, 2012).

2. Large numbers of chemicals have not been studied adequately for their carcinogenic potential. This is well known to be the case. For example, in Europe, around 100,000 industrial chemicals introduced to the market prior to 1981 (referred to as "existing chemicals") have not be assessed for their risk. Concerns about this dire situation have stimulated a new EU regulatory framework for industrial chemicals called REACH, that was launched in that the European Commission describes as "an integrated system for the registration, evaluation, authorisation and restriction of chemicals. Its objective is to improve the protection of human health and the environment whilst maintaining competitiveness and strengthening the spirit of innovation in Europe's chemicals industry."[4] It will be years before all the chemicals in use are evaluated, and they will continue to evaluated in isolation, rather than in the mixtures to which we are exposed. Moreover, REACH requires the manufacturers to evaluate their own chemicals following specific guidelines. Given the somewhat chequered history of the chemical industry, exemplified by the occurrence and subsequent handling of the Bhopal disaster in India in 1984,[5] this does not necessarily ensure assessments will be reliable. Regardless, REACH is at least a step in the right direction for public health, and it is promoting approaches to risk assessment that do not involve animal testing.

3. Proving cause and effect is extremely difficult. Proof in scientific terms means proving an unequivocal cause and effect relationship based on the best available evidence, or, on the balance of all the available evidence. In research papers, the latter is often referred to as the totality of evidence. The fact it took over 30 years of extremely well-funded research to prove that smoking causes cancer is an example of how challenging establishing proof of carcinogenesis can be. To prove that a chemical is a carcinogen, it needs to be demonstrated—without any doubt—that exposure to a given chemical, based on the best available evidence, or the totality of evidence, causes cancer in humans. Showing rats or mice get cancer following exposure to high doses of a given chemical, even if this is done over and over again, including in different strains, including ones that are not highly susceptible to cancer, wouldn't be proof enough. But it might be enough to have the chemical classified as a probable or possible carcinogen. Retrospective observational studies on human populations can be used to show very strong associations, and these have been the primary way of identifying occupationally-exposed carcinogens, such as asbestos, benzene, or even the fact that low intakes of fruit and vegetable or heavy alcohol consumption are associated with increased risk of cancer (Ezzati and Riboli 2012).

   Another complication is latency. A considerable period of time typically elapses between exposures and the development of cancer—this 'delayed effect' making it even more difficult to establish cause and effect.

   It is noteworthy that fewer and fewer animal studies are being performed because of

concerns about animal cruelty, an issue that was rightly put on the international agenda by the anti-vivisection community. The reality is that we are never exposed to chemicals in isolation. We are always exposed to chemicals in mixtures, even though the dosage or frequency of exposure of one particular chemical may ultimately be found to be the trigger. But this means, out of the 'noise' from all of our exposure, probably only the most potent carcinogens get identified and then classified as proven, probable or possible carcinogens. Humans, it has to be said, are guinea pigs in a huge uncontrolled experiment.

[1] International Agency for Research on Cancer website: www.iarc.fr.

[2] Boseley S. Renowned cancer scientist was paid by chemical firm for 20 years. Guardian newspaper, 8 December 2008: *http://www.guardian.co.uk/science/2006/dec/08/smoking.frontpagenews [*last accessed 15 December 2012].

[3] American Cancer Society; Heredity and Cancer: *http://www.cancer.org/cancer/cancercauses/geneticsandcancer/heredity-and-cancer* [last accessed 15 December 2012].

[4] Regulatory framework for the management of chemicals (REACH), European Chemicals Agency: *http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/chemical_products/l21282_en.htm* [last accessed 15 December 2012].

[5] The Bhopal Medical Appeal: *www.bhopal.org* [last accessed 15 December 2012].