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How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease

Smoking as a contributor to the cause of occupational lung cancer has been taken to court, but the situation is unclear. The detailed mechanisms now being worked on will allow greater certainty in the future, but not yet. In the alternate, inflammation could be used as a catch-all mechanism. Any cause or contributor to inflammation could be cited as a contributory cause. Cancer is indivisible, BUT, details of the mechanism could provide defences based on timing of exposure, and *de minimis*.

Smoking causes cardiovascular disease. Occupational or product contributions to this would be possible. Indivisible and divisible outcomes are both possible. Likely claims involving smoking would be when fine dust exposure is alleged to be a cause of indivisible heart disease. More speculative would occupational causes of debilitating high blood pressure or angina; both of which are divisible.

Conclusions in the report:

> *Every year, thousands of nonsmokers die from heart disease and lung cancer, and hundreds of thousands of children suffer from respiratory infections because of exposure to secondhand smoke. There is no risk-free level of exposure to tobacco smoke, and there is no safe tobacco product.*
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> *This new Surgeon General's report describes in detail the ways tobacco smoke damages every organ in the body and causes disease and death.*
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> *The way tobacco is grown, mixed, and processed today has made cigarettes more addictive than ever before. Because of this, the majority of smokers who try to quit on their own typically require many attempts. It is imperative that we use this information to prevent initiation, make tobacco products less addictive, and provide access to treatments and services to help smokers quit successfully.*
>
> *The risk and severity of many adverse health outcomes caused by smoking are directly related to the duration and level of exposure to tobacco smoke. Sustained use and long-term exposures to tobacco smoke are due to the powerfully addicting effects of tobacco products.*
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> *Low levels of exposure, including exposures to secondhand tobacco smoke, lead to a rapid and sharp increase in endothelial dysfunction and inflammation, which are implicated in acute cardiovascular events and thrombosis.*

In 2009, the *Family Smoking Prevention and Tobacco Control Act* [Public Law 111-31] was enacted, giving FDA explicit regulatory authority over tobacco products (nicotine in various products is extracted from tobacco).

The new Surgeon General's report extends to 727 pages. There were over 130 contributors and reviewers.

Of generic interest is information on the disease process for lung cancer, lung fibrosis and cardiovascular disease. There are many causes of lung cancer, fibrosis and CVD; the role of smoking in these must be known if there is to be accurate assessment of synergy or cumulative effects.

Understanding of mechanism, including addictive extension of exposure, could also lead to interventions. If these interventions are practicable and fall within the scope of a duty holder then liability exposure may be changed. For example, duty of care for dust exposure could be different for smokers.

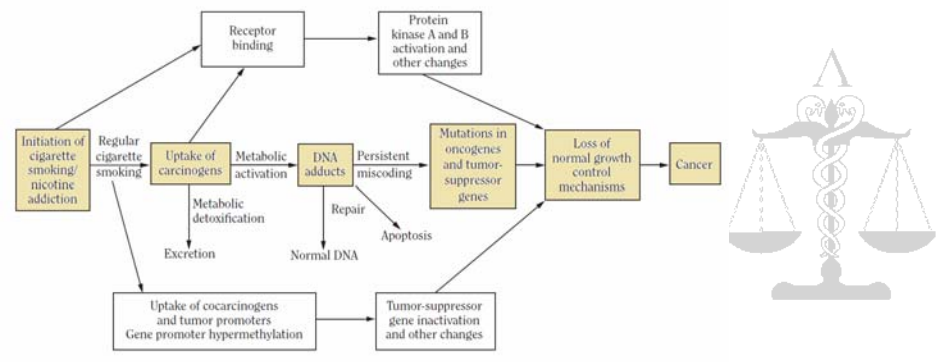
Of concern in the UK is the developing theory of material contribution. With 10 cancers and 9 chronic diseases attributed to tobacco smoke the opportunity for cumulative and simultaneous contributions to causation is very significant. A 'Mode of Action' test of causation would increase the opportunity for material contribution to be found. 'Mode of action' is to 'mechanism of action' what 'plausible' is to 'probable'. Does the Surgeon General use 'Mode of Action' or mechanism, as the basis for deciding causation?

The courts have shown an interest in assigning the greater burden of responsibility to the employer who broke a duty of care than to the smoker who was responsible for the greater part of the risk e.g. *Badger v MOD, Radar* database entry 5#11 5#12 12 and *Shortell v Bical, Radar* database entry 8#5-6 31. Understanding mechanism is vital to understanding liability exposure.

Different mechanisms would fall under different legal precedents. The list includes *Bonnington, McGhee, Wilsher, Badger, Bailey, Barker, Gregg v Scott, Fairchild, Hotson, Holtby, Sienkiewicz, XYZ, Novartis* and the recent EL triggers case. For example, exposure to multiple mutagens would be under *Wilsher* if

they each operated independently and under *McGhee* if they somehow co-operated. Chronic inflammation would be added to by any and all irritants, *Bailey* might be cited if the outcome is indivisible, *Holtby* if it is divisible.

Cancer



The figure illustrates the known steps in the disaese process, but does not make explicit the point that cancer developes through genetically distinct stages, though it is possible that these stages could occur at one go, this is extremely unlikely. In practice, it is much more likley that loss of normal mechanisms is followed by going back to the beginning for the next change to be acquired. The text of the report describes in great detail the necessary stages and what is known about them. Some stages are needed before others.

The key points are:

- The greater the exposure, the greater the risk of lung cancer, and other cancers.

- That carcinogens are delivered into the body by tobacco smoke is evidenced by their appearance in the urine of smokers. Some are specific to tobacco smoke. The total exposure of smokers to known carcinogens is approximately 1.4 to 2.2 milligrams (mg) per cigarette. Some carcinogens are more potent than others.

- Carcinogens combine with DNA following a process of activation by the body. The combination is called an adduct. Higher adduct levels are associated with higher risk of lung cancer. Smokers have higher levels of adducts in all tissue types. Chemicals which are known to remove adducts reduce the rate of DNA damage in living cells.

- It is suggested that adduct formation is a necessary precursor to DNA damage. This is a new and challenging area of research in humans; adduct formation rates are very low and therefore difficult to detect. Adducts would tend to damage DNA at specific sites. If damage at those sites is observed in full-blown cancer the suggestion would be that the tobacco carcinogen could be responsible. [This is an area of speculation; the number of site specific adducts observed to date is small.]

- DNA adducts *per se* are not mutations and can be removed by various DNA repair mechanisms in cells. During cell division, adducts can cause heritable mutations.

- *TP53* gene mutations are found in approximately 40 percent of human lung cancers; these mutations are generally more common in smokers than in non-smokers. One mutation in this gene is called G→T transversion; various carcinogen- DNA adducts can produce G→T transversions and even similar spectra of mutations. [But the evidence of one effect ought not to lead to generalisations!]

- Some of the specific DNA damage done by carcinogens is directly observed in full blown lung cancer. [In our view this is a potentially misleading observation; only those changes which are amplified in the final stage of cancer will be observed, countless other changes caused by countless other mechanisms may be lost or be bellow the detection threshold. And, the specific DNA damage observed could be caused by any damage mechanism.]

- DNA repair mechanisms and the process of removal of damaged DNA are both impeded in smokers.

Comment on lung cancer

The story is coherent and there is evidence at each stage. The evidence is fragmentary and incomplete, but promising. That components of cigarette smoke could deliver the changes observed at each stage has been demonstrated in experiments on cells if not yet in complex organisms.

Evidence of the retention of the tobacco carcinogen at the site of the DNA damage would increase the credibility of this story but is likely to be very difficult to observe. Without evidence that the damage seen in full-blown cancer can only be caused by tobacco smoke carcinogens, it can always be argued that the damage occurred otherwise.

By moving away from epidemiological associations to detailed mechanistic steps the argument for tobacco smoke carcingenicity is strengthened.

The risk in terms of material contribution is arguable at all stages. Initiation by carcinogen x could be retained or left unrepaired because of interference by tobacco smoke. Initiation by tobacco smoke could be promoted by promoter x. 'Could be', would be converted to fact only by detailed analysis of each situation.

Cancer developes though several stages. A new form of DNA damage and retention mechanism is required at *each* stage while retaining the earlier changes. If a tobacco specific effect only occurred after stage n, then what is being argued is that progression is being made more likely. If tobacco smoke is capable of delivering the change needed at each stage then no other carcinogen is required. An understanding of this in any given case would be aided by relative potency factors, timing of exposure and health history.

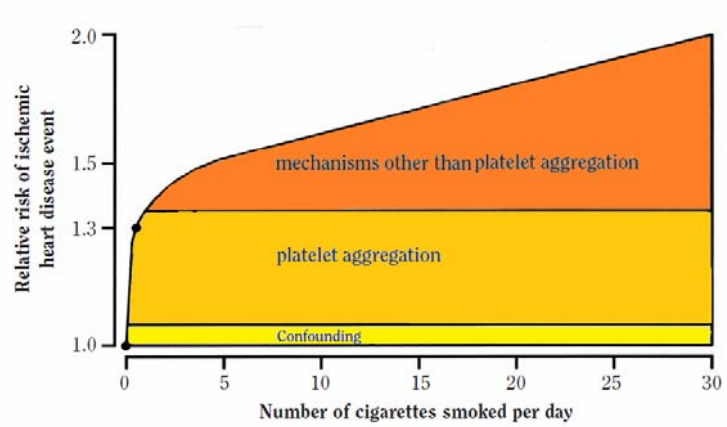
Chronic inflammation can lead to DNA damage (indeed DNA damage occurs even under normal conditions, but happens more often when there is inflammation). If tobacco smoke leads to chronic inflammation then there may be little to be gained by looking for very detailed mechanism. This would be a Mode of Action argument.

The effects of alcohol and asbestos are also discussed in the report. For alcohol there are some mechanisms which would amplify the carcinogenic potential of tobacco smoke. No such knowledge is available for the effect of asbestos.

Cardiovascular disease

The key points are:

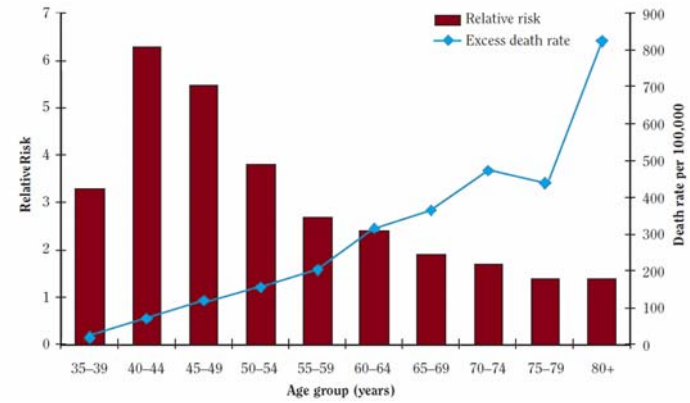
- The greater the exposure, the greater the risk of cardiovascular disease (CVD). The relationship is initially steep and becomes less steep at very high exposures. Given the habit, an appropriate measure of exposure is number smoked per day.



Blood clots are the principle agent in CVD events; they block blood vessels. Platelet aggregation is a measure of the tendency to form blood clots. The excess risk due to platelet aggregation is pretty constant across all levels of exposure, and could explain why passive smoking seems to have a disproportionate effect. Other mechanisms such as damage to blood vessels (leading to wall thickening and clot formation) and lipid concentration increase become significant at higher intensity of exposure.

- The greater the exposure the greater the likelihood of blood clots.
- Blood vessel walls are directly injured or become dysfunctional following exposure. Injury to vessel walls is associated with increased risk of CVD.

- Blood vessel walls become inflammed following exposure, inflammation is associated with increased risk of CVD.
- Smokers tend to have higher cholesterol levels. [and lower HDL levels].
- Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with or without coronary heart disease.
- The evidence to date does not establish that a reduction of cigarette consumption (that is, smoking fewer cigarettes per day) reduces the risks of cardiovascular disease. [that this is contrary to the first and sixth bullet points is not commented on.]



When CVD death rates are low the relative risk effect of smoking in men is high simply because not many other causes of CVD are effective by that age. Attribution of CVD to smoking is much more likely in younger men. The RR for death from a cerebrovascular disease among smokers was substantially elevated among younger smokers (RR = 4 to 5).

Comment on CVD
Several known disease mechanisms for CVD are associated with smoking. The potential for material contribution is direct (no need for an analysis of 'could be'). Disease which is actually caused by smoking can be added to by other exposures, stages in the disease can be added to by other exposures, the effect of other exposures can be made worse by smoking.

A key question is whether or not we are dealing with an indivisible harm. Death from CVD is clearly indivisible. Given the cummulative nature of the disease process which leads to that point other measures of harm e.g. debilitating high blood pressure, e.g. debilitating angina etc could be regarded as divisible.

Duty of care?

> *There are ways to lower the concentrations of toxic constituents in cigarette smoke, although additional research is needed to determine the levels of reduction required for achievement of measurable and biologically relevant decreases in delivery of these constituents to the smoker. Such approaches include controls over tobacco growing and curing; the types of tobacco used in the filler, including the use of reconstituted tobacco; the use of additives such as menthol; and the design of the cigarette.*
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> *It would also be possible to develop different standards of occupational exposure to apply to smokers.*