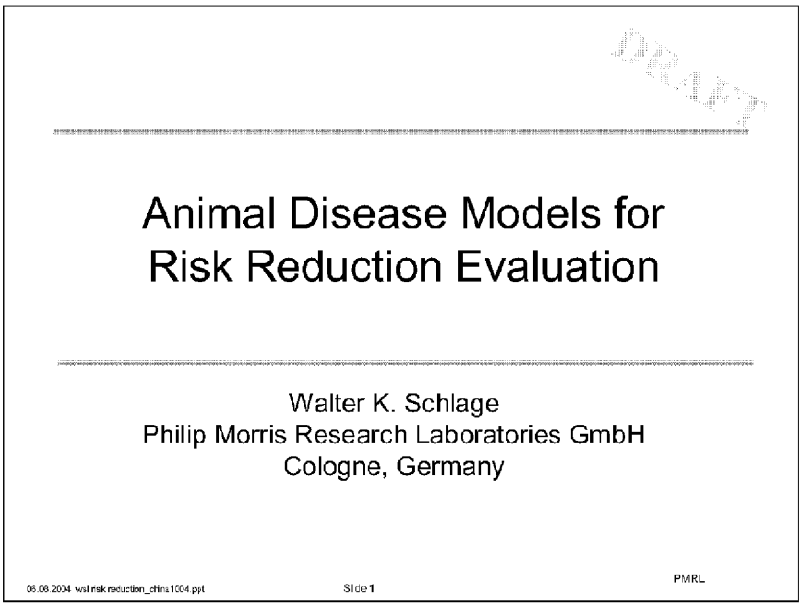

Ladies and Gentlemen, Mr. Chairman:

First, I would like to thank the organizers for inviting me, and particularly Mr. Zia for your hospitality.

In my presentation, I would like to give you an overview on an approach to utilize animal models in the process of risk reduction evaluation.

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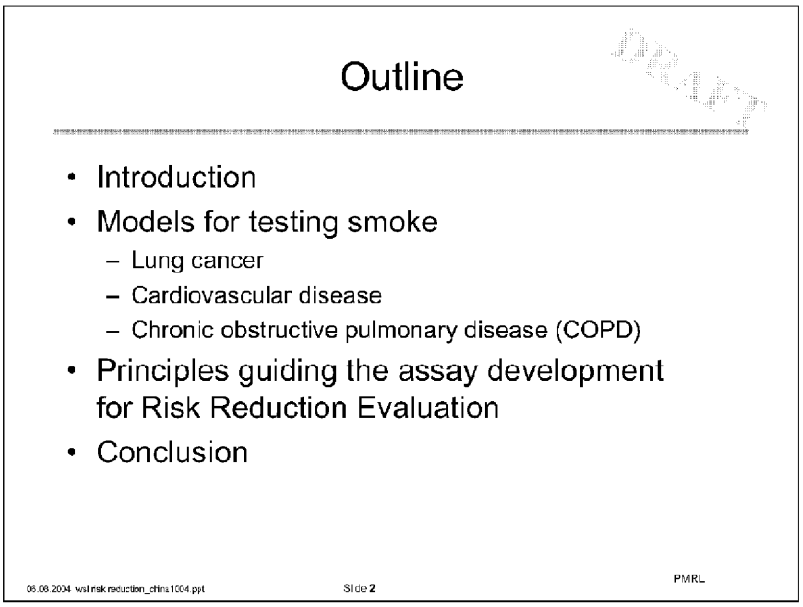

Here is an outline of my presentation.

As an introduction and to illustrate the objective of this presentation, I will explain you the rationale for the choice of animal models of certain human diseases related to cigarette smoking, and how they can be implemented in our non-clinical risk evaluation framework.

In the main part, I will give you examples of animal models that are thought to relate to distinct aspects of the complex diseases, lung cancer, cardiovascular disease, and chronic obstructive pulmonary disease (or COPD). Then, I will show how the disease models can be implemented in the principles guiding the assay development for Risk Reduction Evaluation.

Finally, I will close my presentation with a conclusion.

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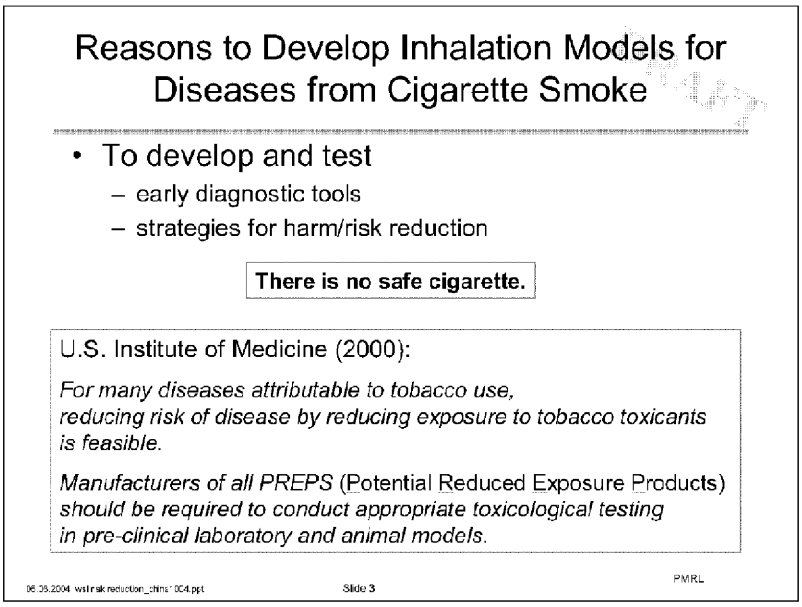

Let me first explain why experimental models for the smoking-related diseases are necessary in our non-clinical testing. These models should be preferentially, inhalation models for obvious reasons.

An essential role for disease models is to provide anchoring points for the development and testing of specific biomarkers as early diagnostic tools For doing that, one needs to understand the mode of action in order to evaluate the causality in the sequence of events and damages leading to the complex phenotype of the final disease. This is mandatory because the biomarkers that can be derived from diseased humans are typically related to relatively late steps in the development of the disease, and in addition may be biased by nonspecific systemic and secondary reactions of the patient.

Within the objectives of this presentation, I will focus on the strategies for harm/risk reduction:

As we all know, there is no safe cigarette – nevertheless, the reduction of adverse health effects of smoking is an indispensable goal for cigarette manufacturers. This is confirmed by the U.S. Institute of Medicine as cited here: *[green box]*

The need for mechanistic research is also stressed in the U.S. Surgeon General's Report, 2004.

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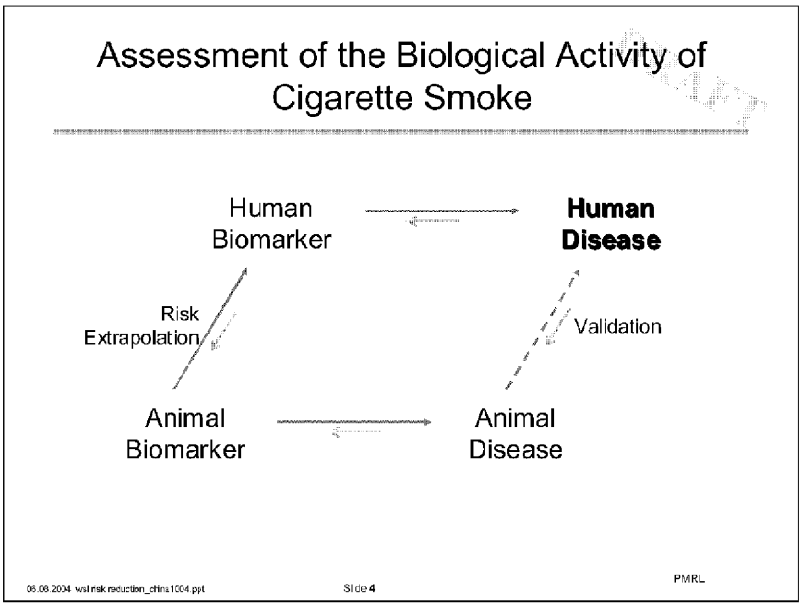

This parallelogram shows the typical relationships and extrapolations that can theoretically be made between human disease and the various levels of model systems. The green arrows depict the direction of possible extrapolations. Ideally, results from animal disease models could be used to extrapolate potential risks for the same type of disease in the human population, **given the model shows a quantitative response** to the test substance. Even more important is the fact that prior to this application the model has been validated to reflect the hallmarks of human disease (shown by the violet arrows).

Similarly, animal biomarker measurements and in vitro results can be used to extrapolate for the potential results in animal disease models, if they have been validated.

On the other branch of this parallelogram, validated human disease biomarkers may be used to extrapolate the risk of disease, although they may occur only after the disease has developed to an advanced stage (e.g., classical tumor markers like alpha-fetoprotein or carcino-embryonic antigen). Theoretically, the results from animal biomarkers, in vitro assays and/or chemical analyses may also be extrapolated via the homologous human biomarkers to the human disease.

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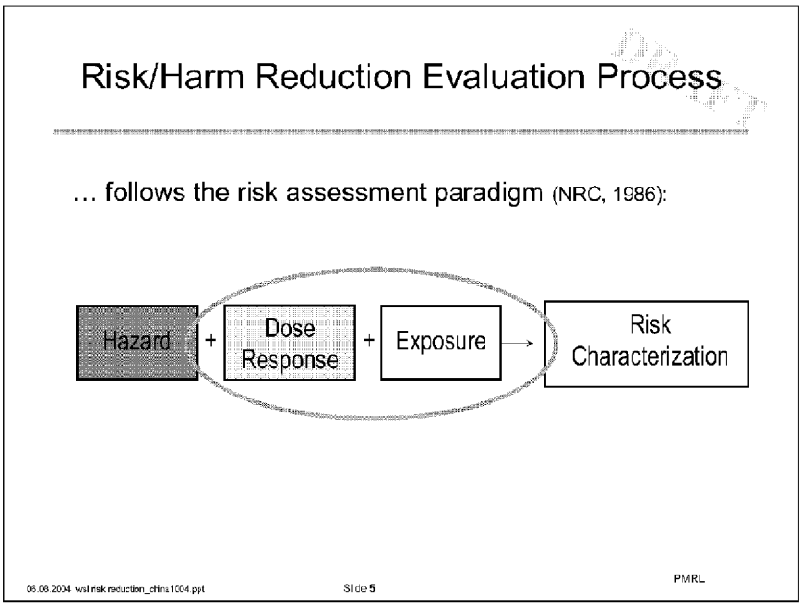

As I already stressed in my previous slide, our models for risk reduction evaluation must respond to cigarette smoke in a dose-response fashion, because according to the common risk assessment paradigm dose response and exposure are needed for the risk characterization, e.g., of a newly developed PREP.

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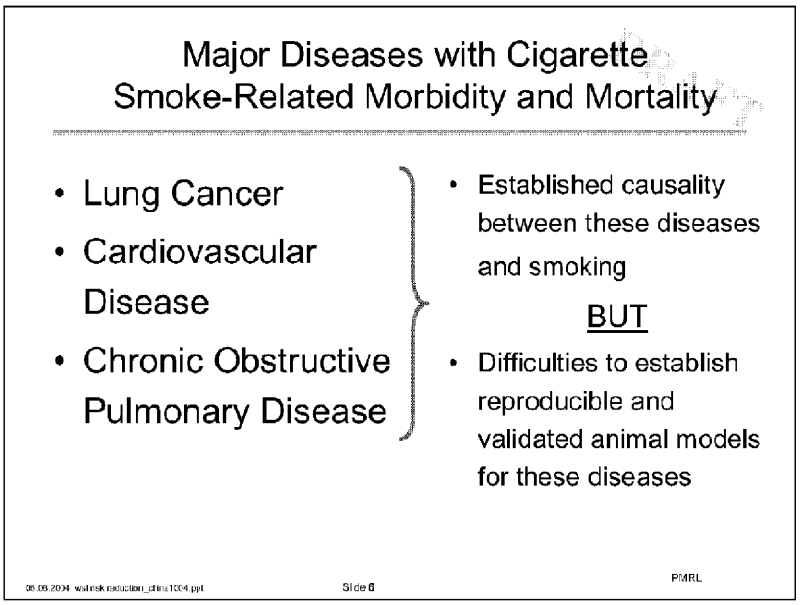

In my presentation, I will focus on the 3 major diseas that, among others, largely contribute to smoking-related morbidity and mortality. In the 2004 U.S. Surgeon General's Report, a recent review can be found.

Although the causality between these diseases and smoking is established, there is obviously a lack in reproducible and validated animal models for these diseases that would allow for a reasonable non-clinical, toxicologically based evidence of reduced risk that could be anticipated for PREPs

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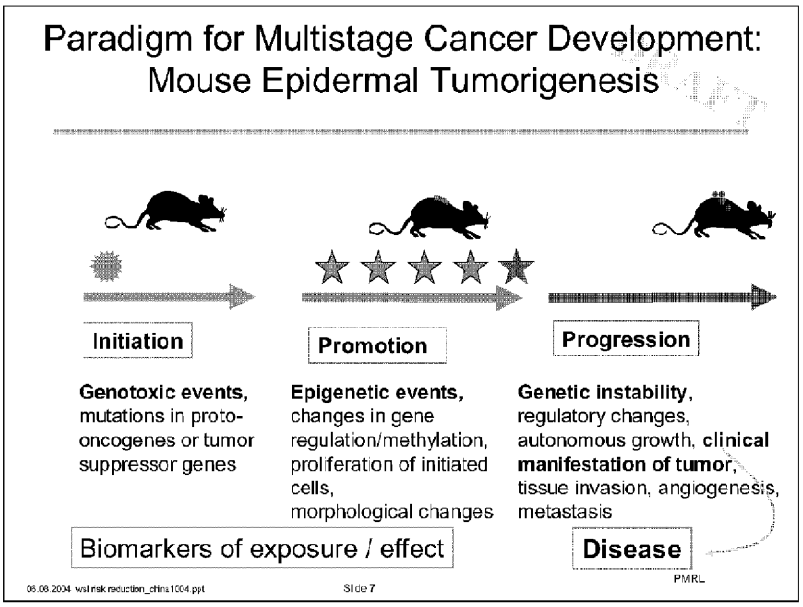

Basic experimental evidence for the multistage concept has largely been derived from the mouse epidermal tumorigenesis (or skin painting) model. Hundreds of compounds have been identified on an operational basis that are either genotoxic, acting as initiators in this model, or nongenotoxic, acting as tumor promoters (prototype is the phorbol ester PMA or TPA). In contrast to initiation, promoter application has to be repeated over an extended timespan, and single or transient treatment has only reversible effects, e.g., irritation. Finally, the promotion process turns irreversible and tumor development can progress without further promoter treatment.

In view of this known sequence of events, it appears reasonable to make use of „early" biomarkers and surrogate markers for serial assays and screening purposes, instead of waiting until the tumor has formed. It is important to consider that cigarette smoke exerts both initiating and tumor promoter-like effects, when choosing biomarkers for a test battery.

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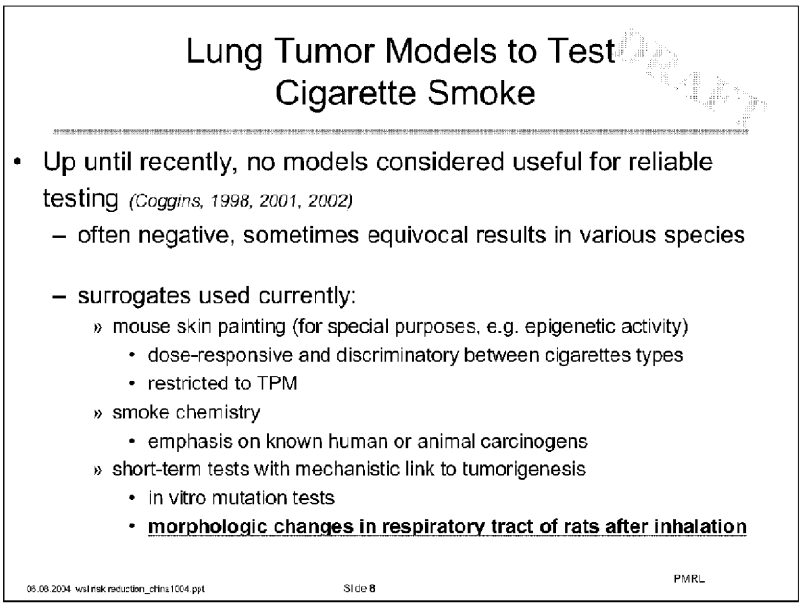

With regard to lung cancer, there is apparently no reproducible and validated animal inhalation model available that develops lung cancer in response to cigarette smoke, in spite of decades of research. There are conflicting, often negative or equivocal results in the published literature.

However, a few promising inhalation studies have been reported recently, and I will come back to them in a few minutes.

For the time being, many different surrogate assays have been applied in cigarette smoke testing. The classical skin painting, as first applied by Hoffmann & Wynder, can detect epigenetic, i.e., tumor promoter-like activity. This model provides dose-response relationships and allows discrimination of cigarette types, however, it is restricted to the total particulate matter (TPM) fraction of the smoke. Another surrogate approach is to use smoke chemistry of known carcinogens to extrapolate cancer risks.

There are also many established short-term tests, e.g., for mutagenicity or cytotoxicity testing, that can be linked to tumorigenesis.

A widely applied surrogate approach for lung tumorigenicity in inhalation assays is to determine the morphologic changes in the respiratory tract of rats after smoke inhalation. As I will show you in the next few slides, these effects occur in a dose-responsive manner and can be used for cigarette discrimination.

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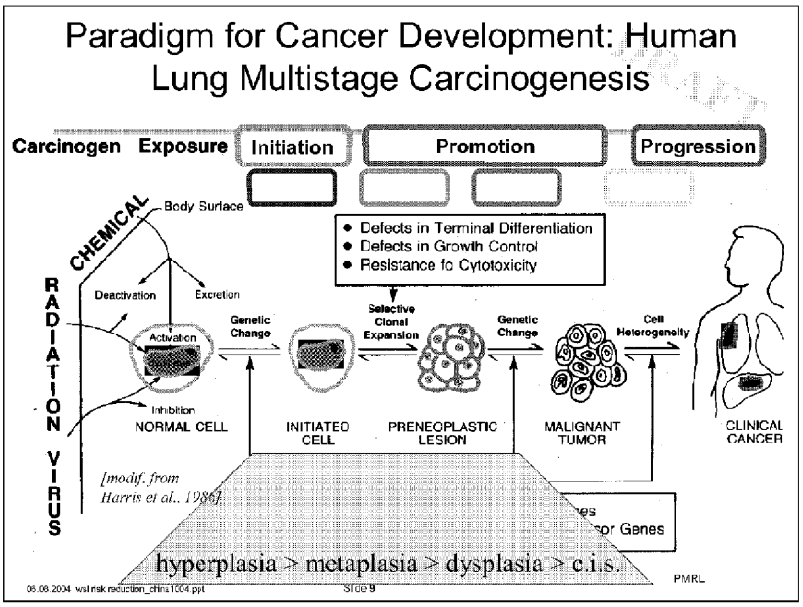

This is a schematic representation of the development of human lung cancer according to the multistage concept. You can see the sequence of events starting with the initiation, which is believed to be a mutational event, and the selective clonal expansion of the initiated cell population under the influence of a chronic, epigenetic promoter activity. After prolonged promoter exposure, additional genetic changes may occur which cause an autonomous progression into a malignant tumor mass. Moolgavkar and Knudson (1981) have applied such a model to fit human epidemiological data. This model also appears to be consistent with recent molecular findings.

In the yellow box, you can see the classical "preneoplastic" changes associated with human lung carcinogenesis. This sequence of hyperplasia – metaplasia – dysplasia –carcinoma has been shown to precede certain neoplastic lesions in the human respiratory tract, and therefore these changes can be regarded as intermediate biomarkers of tumorigenesis.

In rodent inhalation models, these histological changes do also occur in response to smoking, but in most investigations they were reversible during exposure-free post-inhalation periods and did not progress to neoplastic lesions. They rather appeared to represent adaptive responses to the irritative activity of smoke. Hopefully, we will learn more about a potential link of such lesions to lung tumors if the promising new lung tumor models I will refer to later on can be reproduced and linked to mechanistic investigations.

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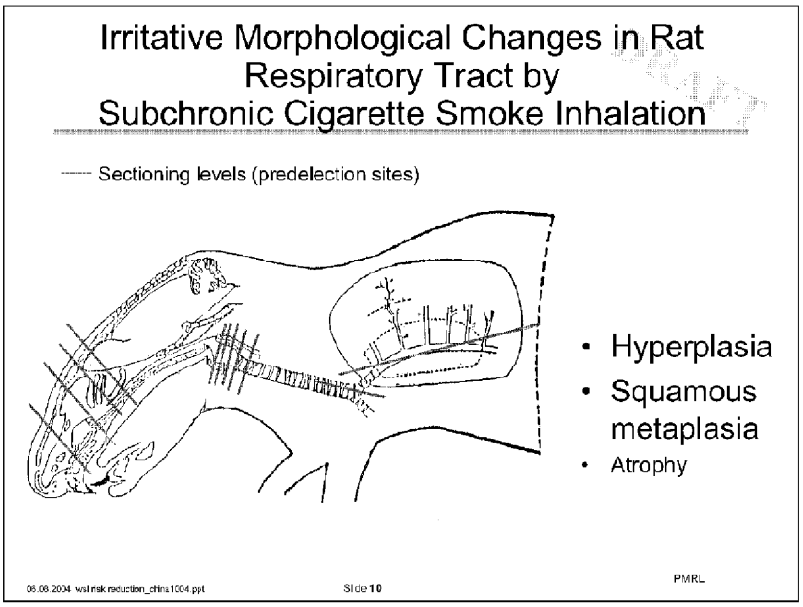

This slide depicts the predilection sites at which we routinely take sections for comparative histopathological evaluation of smoke effects.

Up to 4 defined levels are taken from the nasal cavity, up to four levels in the larynx, one tracheal ring, the tracheal bifurcation, and the left lung.

Hyperplasia of reserve cells or goblet cells and squamous metaplasia of the pseudostratified epithelia at the various sites are the most common changes, sometimes also atrophy, e.g., of the olfactory epithelium in the nasal cavity.

As I already mentioned, these effects are reversible after subchronic exposure and apparently do not progress if the inhalation exposure is extended.

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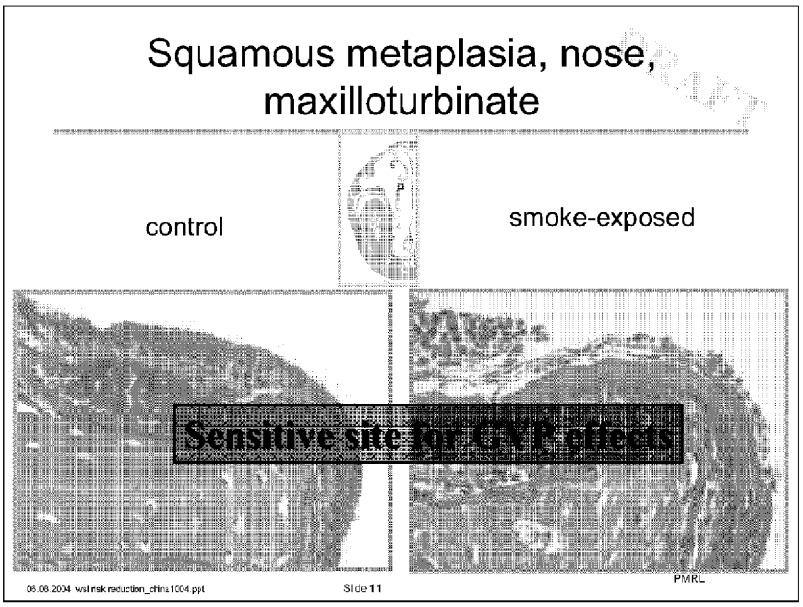

This example shows a very sensitive site for gas-vapor phase effects in the anterior part of the nasal cavity, especially on the maxilloturbinates. You can see the squamous metaplasia of the respiratory epithelium, with signs of cornification.

Again, this effect is reversible during a postexposure recovery period. No signs of progression have been observed in our subchronic inhalation studies.

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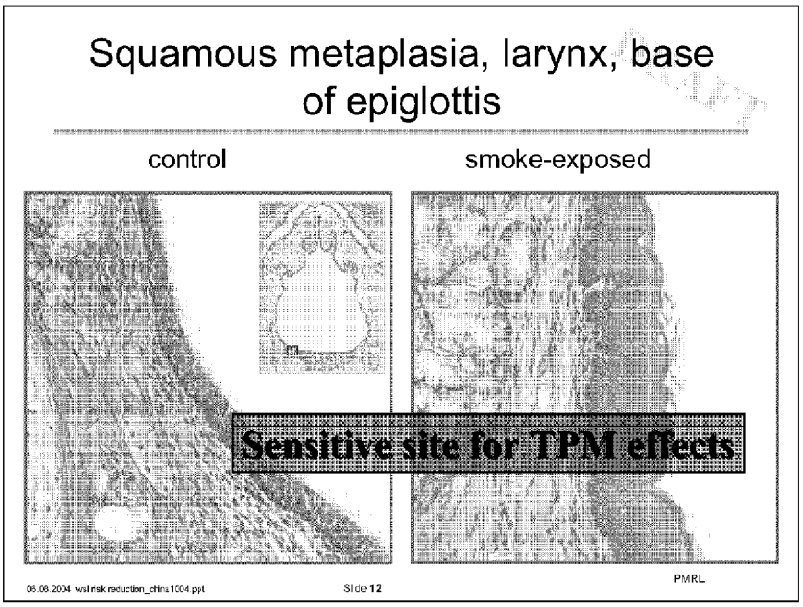

Here you can see squamous metaplasia of the pseudostratified epithelium at the most sensitive site of the rat respiratory tract, the base of epiglottis in the larynx. Dose-related reactivity to particle exposure can be observed in subchronic inhalation studies from 1 microgram TPM/l onward, and already at medium concs. of MS the saturation of the effect is observed. Complete recovery can be observed within several weeks of postexposure.

It appears that this site is particularly sensitive to TPM effects.

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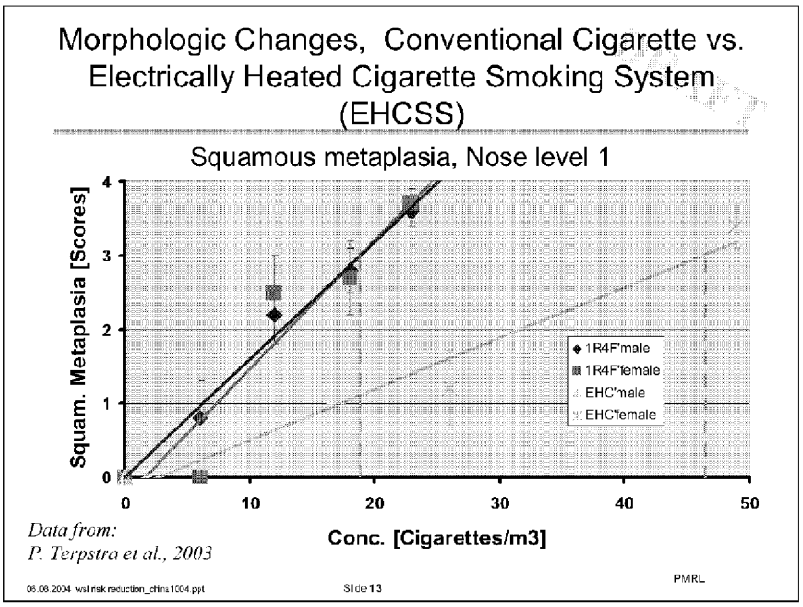

This graph shows a comparison between the 1R4F Standard Reference cigarette and a prototype of an electrically heated cigarette smoking system (EHCSS) with regard to the induction of squamous metaplasia at this sensitive nasal site.

You can clearly see the linear dose responses at and the reduced activity of the EHCSS.

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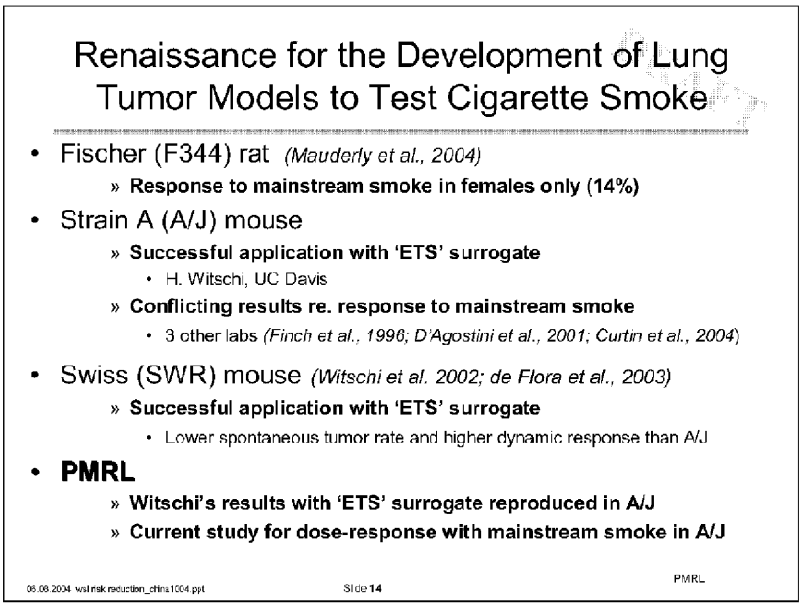

Now I come back to the struggles to develop useful lung tumor models.

I've already mentioned the study published last month by Mauderly and colleagues from Lovelace. They observed a statistically significant lung tumor induction by cigarette smoke in 14% of the female F344 rats, in a 30-months chronic inhalation study. The practical use to discriminate cigarettes, however, is questionable at such a low incidence

For the strain A mice, Peter Witschi and collaborators have shown in series of investigations that the tumor multiplicity increases significantly after exposure to a surrogate for ETS, namely a mixture of diluted sidestream and mainstream smoke. Several attempts in different groups to obtain increased lung tumor multiplicity after mainstream smoke exposure have yielded conflicting results.

Another mouse strain, the Swiss mouse, was also responsive to ETS with an apparently better signal-to-noise ratio than the A/J mouse.

In our own investigations, we could reproduce Witschi's results on the ETS-surrogate and results from our current study on A/J mice exposed to mainstream smoke will be presented at the next SOT meeting.

The next slide shows some results in comparison

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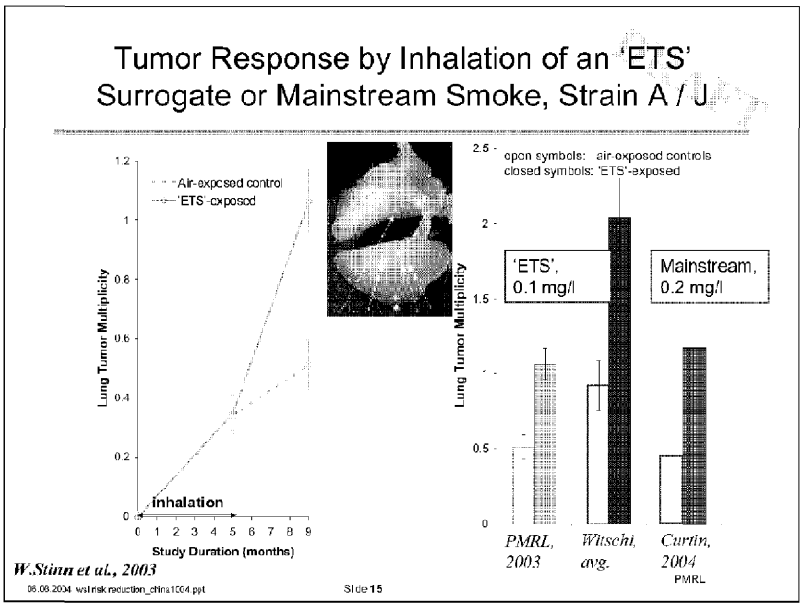

The left hand graph shows our results from a study on A/J mice, where we applied a similar mixture of 11% mainstream smoke and 89% sidestream smoke as it has been used by Witschi. Using also the same 5-mo. exposure – 4 mo. postexposure schedule, we observed no difference in tumor multplicity at the end of the exposure period. Four months later, the tumor multiplicity increased approximately 2-fold higher than in the air-exposed control mice. This has been published by my colleague Walter Stinn. The photo insert shows a lung with multiple tumor nodules.

From the bar graph on the right hand it is obvious that our 2-fold increase in tumor multiplicity following "ETS"-surrogate exposure is consistent with Witschi's average over several studies under similar conditions. His induction factor was also about 2-fold, although he has observed in general a higher background and a higher signal.

Very interestingly, Curtin and colleagues obtained an effect in a similar magnitude in response to mainstream smoke inhalation (red columns).

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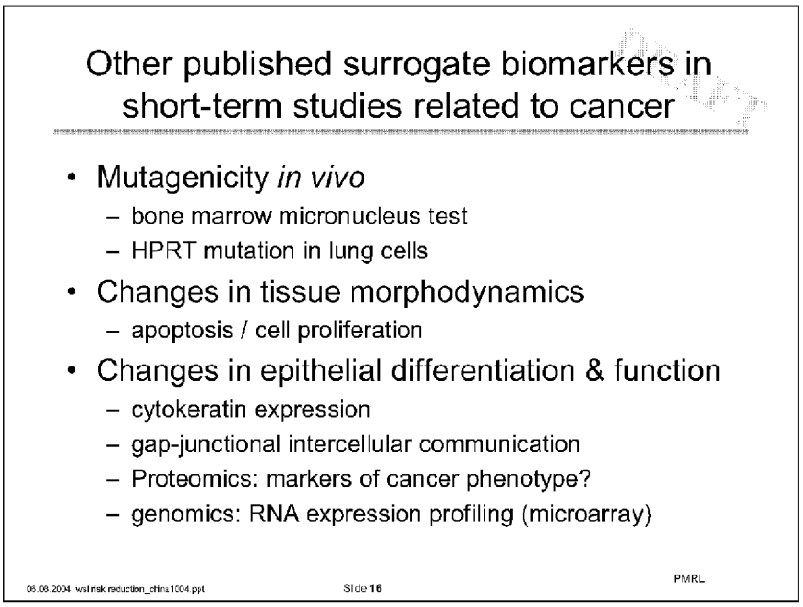

I would like to finish the cancer part with this list of published examples for surrogate biomarkers which might also be of interest in a judgemental matrix for reduced risk evaluation in order to compensate for the lack of an optimal disease model.

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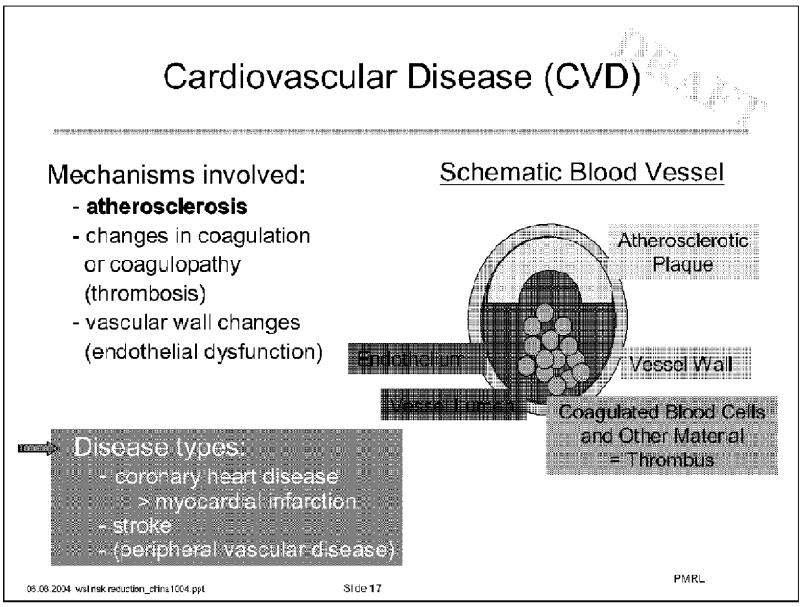

Let me now give you some examples of approaches in the cardiovascular disease area.

As shown in a very simplified fashion on this slide, atherosclerosis, thrombosis, and endothelial dysfunction are key players and may lead to a variety of related diseases, like coronary heart disease, stroke, and peripheral vascular disease.

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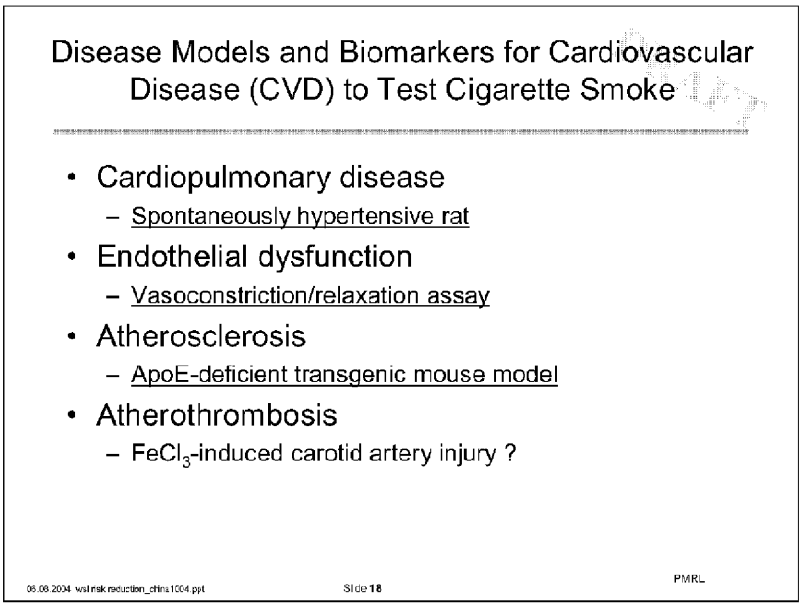

Similarly to the cancer area, there is also no direct disease model reflecting the multiple aspects of human disease.

Therefore, the available models address the key aspects of the disease separately, and I'm going to show you the 3 underlined examples for cardiopulmonary disease, endothelial dysfunction, and atherosclerosis. For atherothrombosis, we are currently exploring, whether the Konstantinides mouse model of iron chloride-induced carotid artery injury may be applicable to cigarette smoke testing.

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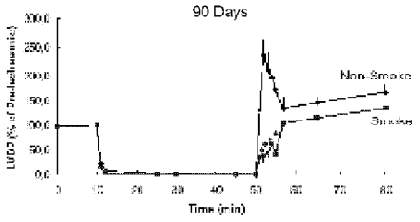
Source: https://www.industrydocuments.ucsf.edu/docs/ffbb0219

The Spontaneously Hypertensive Rat Model for Cardiopulmonary Disease

- Isovolumetric Langendorff perfusion of isolated hearts
- Subchronic (30 d, 60 d, 90 d) CS inhalation induces:
  - Cardiac hypertrophy
  - Decreased coronary resistance
  - Increased force development
  - Reduced Early Post-Ischemic Functional Recovery of Hearts



Schlueter et al., 2002

06.08.2004 wslinskreduction_china1004.ppt Slide 19 PMRL

This slide demonstrates the reduced capability for post-ischemic recovery of hearts from smoke-exposed SH rats, following experimentally induced stroke in the Langendorff-type perfusion model.

Unlike the wildtype Wistar-Kyoto rats, the spontaneously hypertensive rats showed also progressive cardiac hypertrophy and were more sensitive to smoke-induced effects.

It appears that non-compromized rodent strains are relatively resistant to smoke-induced cardiovascular disease symptoms (as it is the case for cancer and COPD as well) under well-defined smoke inhalation exposure conditions.

Therefore, the use of compromized strains, like the SH-rat may improve the development of risk evaluation models

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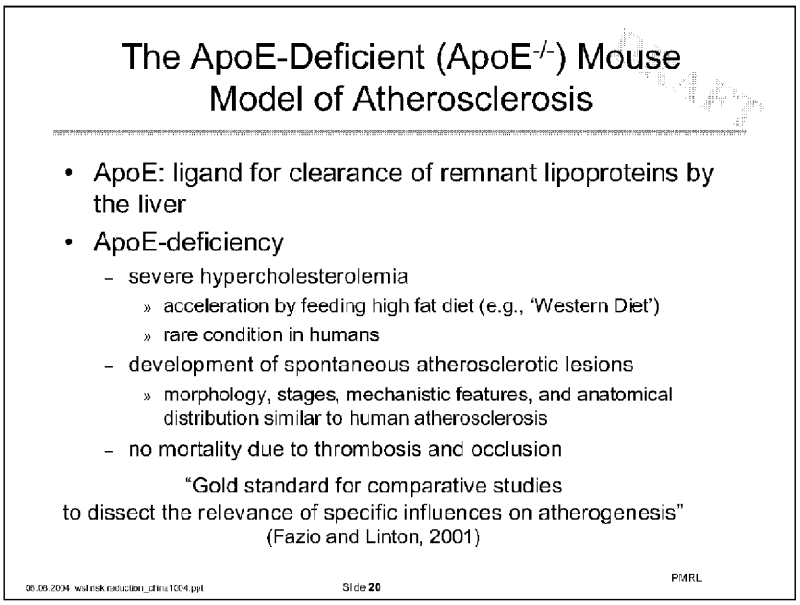

Also my next example is on a compromised animal strain. The transgenic "ApoE mouse" atherosclerosis model has been applied in many pharmaceutical investigations.

The lack of the Apo-lipoprotein E in the liver causes accumulation of remnant lipoproteins in the circulation and thereby

induces severe hypercholesterolemia which can be enhanced by high fat diet. However, this severe hypercholesterolemia is a rare condition in humans, although many of them are exposing themselves to "Western diet".

Nevertheless, the development of early stages of atherosclerosis mimics closely the human pathogenesis.

The major limitation of this model is the apparent lack of progression of the atherosclerotic lesions. The increased formation of unstable, rupturing plaques leading to thrombosis and lethal occlusion has not been observed in this model.

However, the model is regarded as a gold standard for studying the pathomechanisms of atherogenesis.

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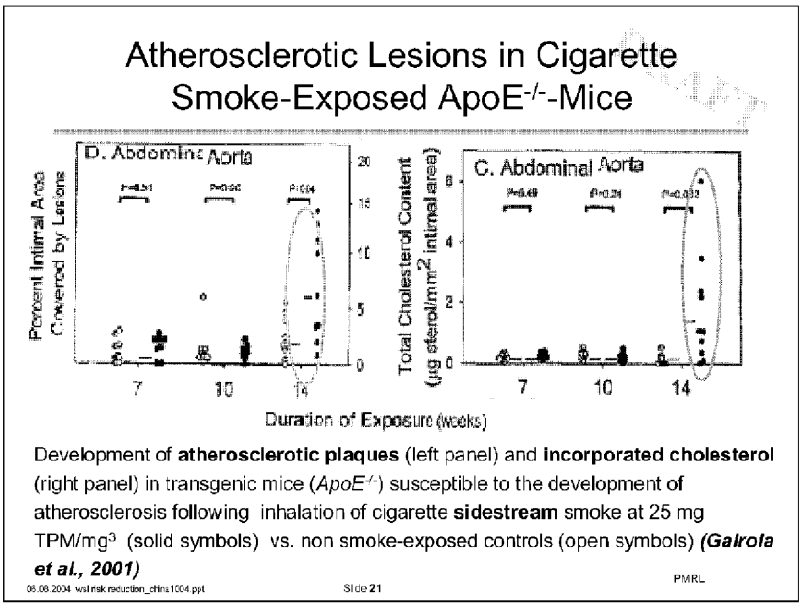

These graphs show results published by Gary Gairola a few years ago concerning the increased atherosclerotic plaque formation (left hand, orange) and cholesterol deposition (right hand, green) in the abdominal aortas from ApoE mice exposed subchronically to cigarette sidestream smoke.

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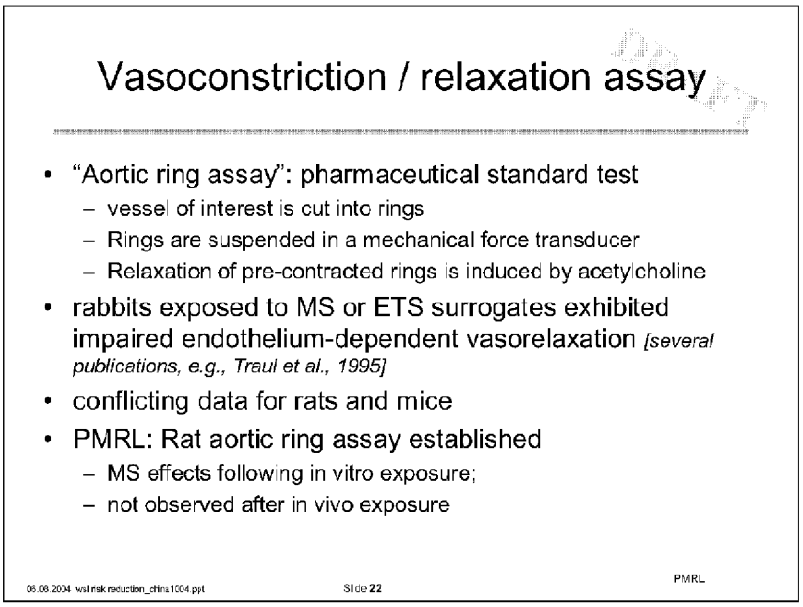

My third example for cardiovascular disease model applications is the classical vasoconstriction assay, also known as the aortic ring assay.

Small rings are cut from the aorta, suspended in a force transducer in an organ bath, and induced to contract. The measurement starts with the induction of relaxation by the stepwise addition of increasing concentrations of, e.g., acetylcholine, in the presence or absence of test substances.

Several publications report on an impairment of endothelium-dependent relaxation in aortic rings from rabbits exposed to smoke, however, conflicting data have been reported for smoke exposed rats and mice.

As I'm going to show you in the next slide, in our hands the assay has performed well if smoke exposure was done in vitro with aqueous smoke extracts. So far, we could not see effects in aortic rings from smoke-exposed rats.

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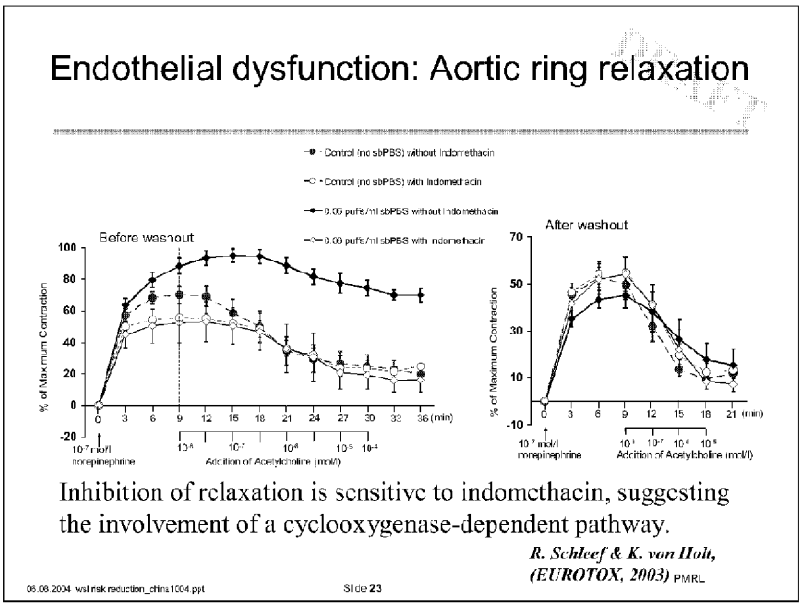

On the left hand graph, the black symbols represent the rings treated with aqueous smoke extract and the blue ones are the controls. The bold curves and filled symbols show that smoke strongly inhibits relaxation, whereas the relaxation comes to control values if the COX-2 inhibitor, indomethacin, is added (open symbols).

This finding suggests that a cyclooxygenase-dependent mechanism is involved in the inhibition of vascular relaxation by aqueous cigarette smoke extract.

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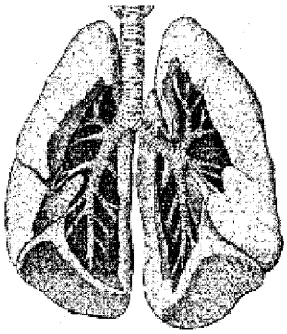
Source: https://www.industrydocuments.ucsf.edu/docs/ffbb0219

Chronic Obstructive Pulmonary Disease (COPD)

- **Chronic (obstructive) bronchitis**
  - progressive and irreversible limitation of airflow often accompanied by
    - » bronchial hyperreactivity,
    - » mucus hypersecretion,
      - Mucous gland hypertrophy (large airways)
      - Goblet cell metaplasia (small airways)
    - » sustained pulmonary inflammation
      - inflammatory infiltrates and fibrosis of walls (small airways)
- **Emphysema**
  - irreversible destruction of alveolar walls by proteolytic enzymes
    - » mediated by pulmonary inflammation (alveolar lumen and interstitium)
      - Elastin degradation



06.06.2004 wslfrisk reduction_chris1 004.ppt Slide 24 PMRL

Now I come to the 3rd major disease, chronic obstructive pulmonary disease. Again, the disease symptoms and mechanisms are multiple. COPD is defined as a progressive and irreversible limitation of airflow which can be associated with bronchial hyperreactivity, mucus hypersecretion, and a sustained pulmonary inflammation.

Two classes of disorders are typically associated with COPD. The first one is chronic obstructive bronchitis. Mucus gland hypertrophy in the large airways and goblet cell metaplasia in the small airways contribute to mucus hypersecretion and the inflammatory processe may lead to fibrosis (small airway disease).

The 2nd disorder, emphysema, is the irreversible destruction of alveolar walls by proteases derived from excess inflammatory cells in the alveolar lumen and in the interstitium (T cell inflammation).

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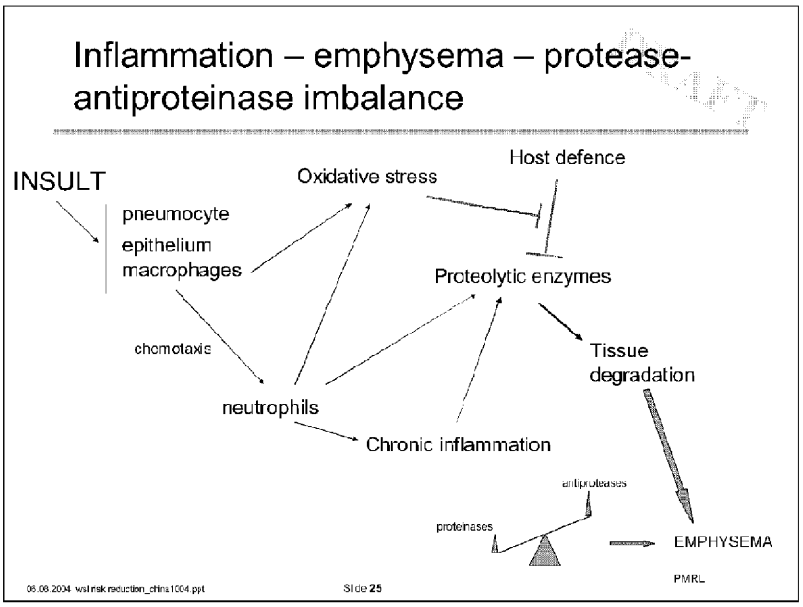

The major players in this complex emphysema scenario are shown in this diagram. Without going into all the details, the point I would like to emphasize is that an insult, e.g. cigarette smoke, can activate alveolar macrophages and pneumocytes directly and indirectly. This causes neutrophil influx. The neutrophils, together with other inflammatory, are responsible for an overshooting oxidant response and protease production (which is no longer just protective). Excess oxidants contribute to additional oxidative stress and excess proteases (MMP's, Alpha-1-antitrypsin) are no longer counterbalanced by endogenous antiproteases. These proteases can digest extracellular matrix proteins and structural proteins like elastin which is crucial for the mechanical properties of the lung alveolar structure.

Notably the balance between the tissue-destructing proteinases and the protective inhibiors of these proteinases is critical for the alveolar wall breakdown leading to emphysema.

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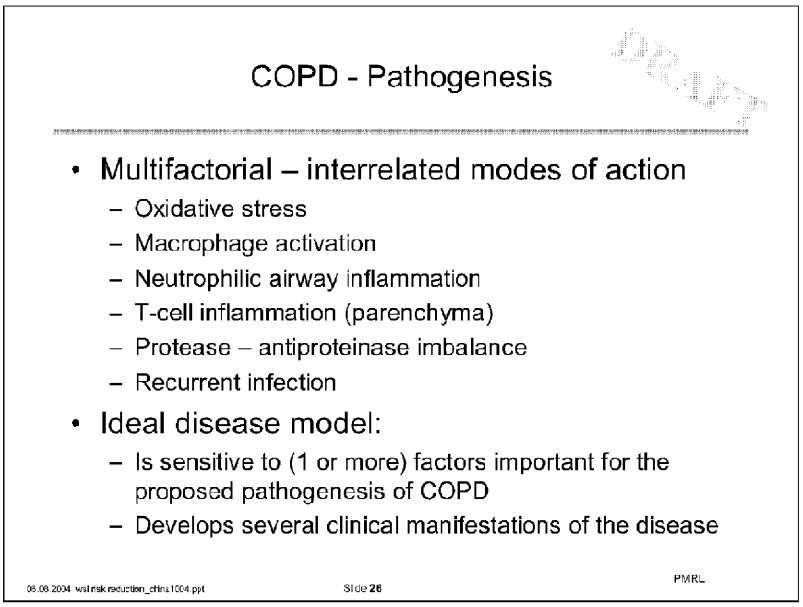

Given the multifactorial nature of COPD pathogenesis – similar to the situation for cancer and CVD – an ideal disease model should reflect as many as possible aspects of pathogenesis, and develop clinical manifestations resembling the human disease, such as airflow obstruction, chronic inflammation, and emphysema.

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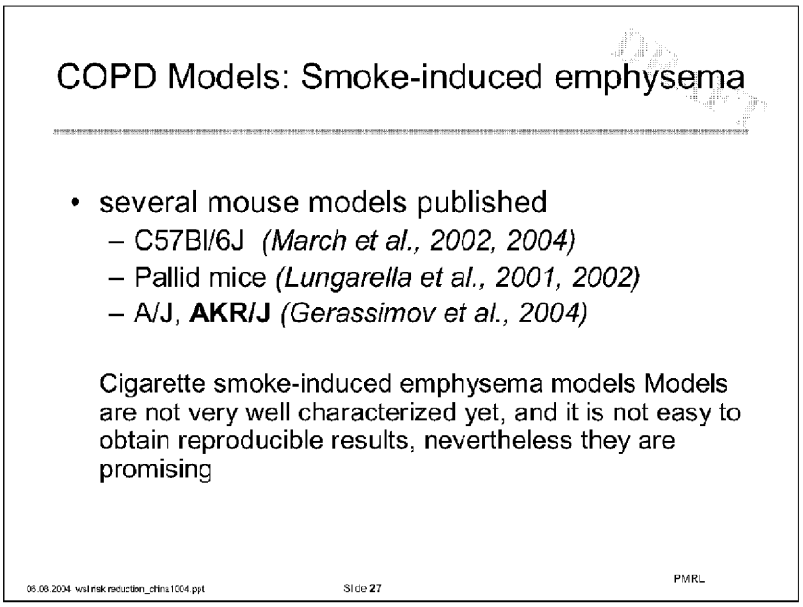

In practice, inflammation models and emphysema models have been described only separately.

Pharmaceutical industry uses smoke-induced emphysema models in which animals are exposed to extremely high concentration of MS from 2R1. In contrast, it has been difficult to induce emphysema in rodents by cigarette smoke for product testing in a dose-responsive and reproducible manner. Several mouse models have been published, like the C57 Black 6, or the more susceptible mutants: "Pallid" with an alpha1-antitrypsin deficiency, and the AKR/J which may reflect more closely the human situation, because they also exhibit decreased lung elastance and a typical inflammatory marker profile including T-cell inflammation.

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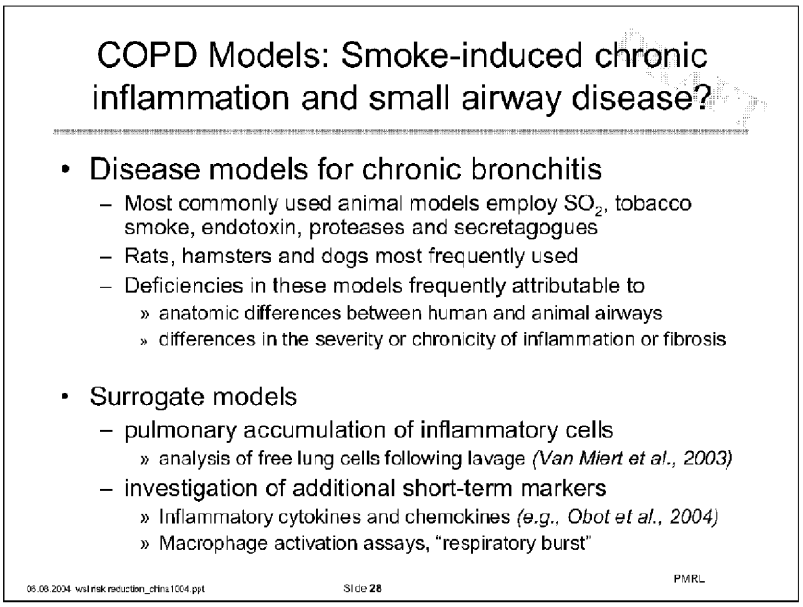

Disease models for chronic bronchitis are available in various animal species, especially after induction with strong agents like SO2 , endotoxin, proteases, and so on. Shortcomings of these models are not only the anatomical differences in the airway architecture, but the apparent lack of the self-sustaining, progressive inflammatory and fibrotic processes. Perhaps the AKR mice with their combined emphysema and inflammatory reaction may become a useful model.

According to our experience, the surrogate approach analysing the pulmonary accumulation of inflammatory cells after subchronic inhalation exposure and of chemokines and cytokines after acute inhalation has become a valuable tool for comparative testing of smoke from different cigarette types because of its good dose response and quantitative reproducibility. However, it must be regarded as a surrogate model, because this inflammation is reversible after stop of exposure and therefore lacks the self-sustaining, progressive aspect of the human pathogenesis.

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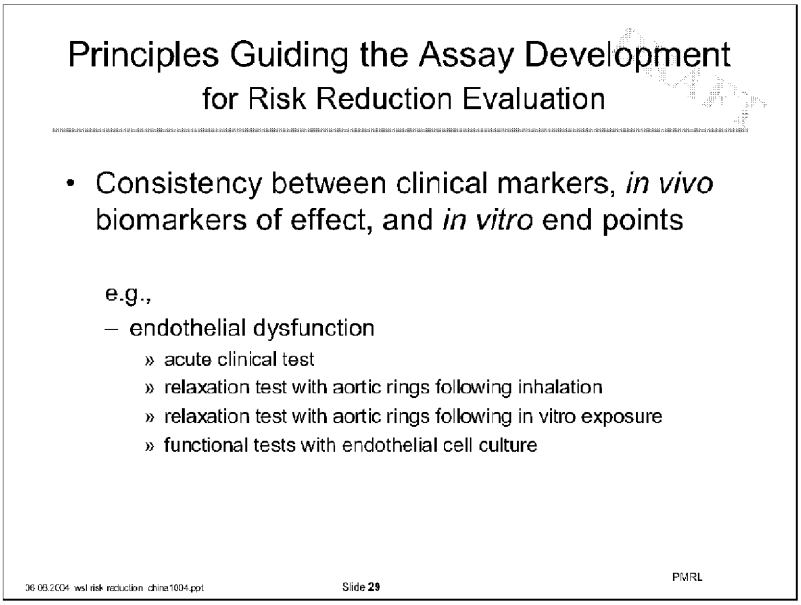

In my last few slides, I would like to come back to the principles guiding our assay development for risk reduction evaluation – in the absence of straight forward disease models, I should add.

One important point is **consistency** between clinical markers, in vivo biomarkers, and in vitro markers used as assay end points. An example is endothelial dysfunction, which can be measured in acute clinical tests, in ex vivo relaxation assays using aortic rings from animals exposed to smoke, in vitro relaxation assays exposing aortic rings from unexposed animals to smoke, and finally in functional tests with endothelial cell cultures, e.g., to test the induction of specific signaling molecules following smoke exposure.

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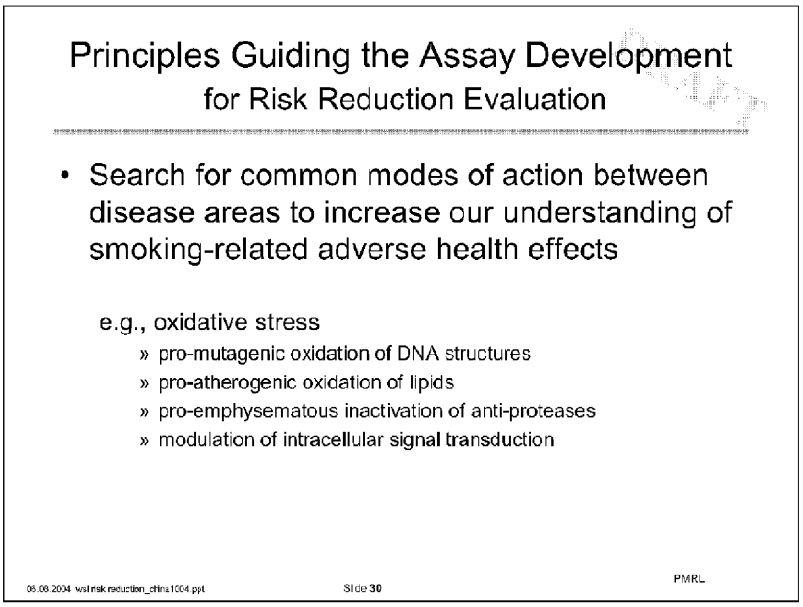

The second principle is the search for common modes of action that may be involved in several disease areas. A good example is the oxidative stress caused by smoke exposure directly or indirectly. Oxidative stress has been shown to act pro-mutagenic by oxidation of DNA structures (8-OHdG etc.); also pro-atherogenic by lipid oxidation, as well as pro-emphysematous by inactivating anti-proteases.

On the level of cellular functions, oxidative stress modulates intracellular signal transduction.

Obviously, the mode of action of such a global player is highly relevant to give guidance for the development of harm-reduced products.

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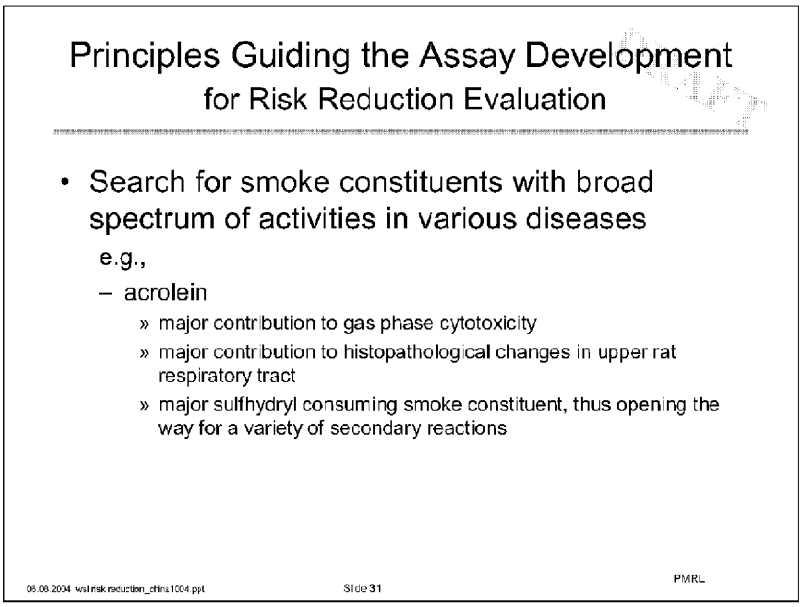

The third principle concerns the search for single smoke constituents with a broad spectrum of activities.

Acrolein is obviously such a bad guy. It has been experimentally shown by us and others that acrolein contributes a major part of the gas phase cytotoxicity, and to the histopathological changes in the upper respiratory tract of rodents. On a molecular level, acrolein is a major SH-consuming agent, which may encounter all kinds of secondary reactions.

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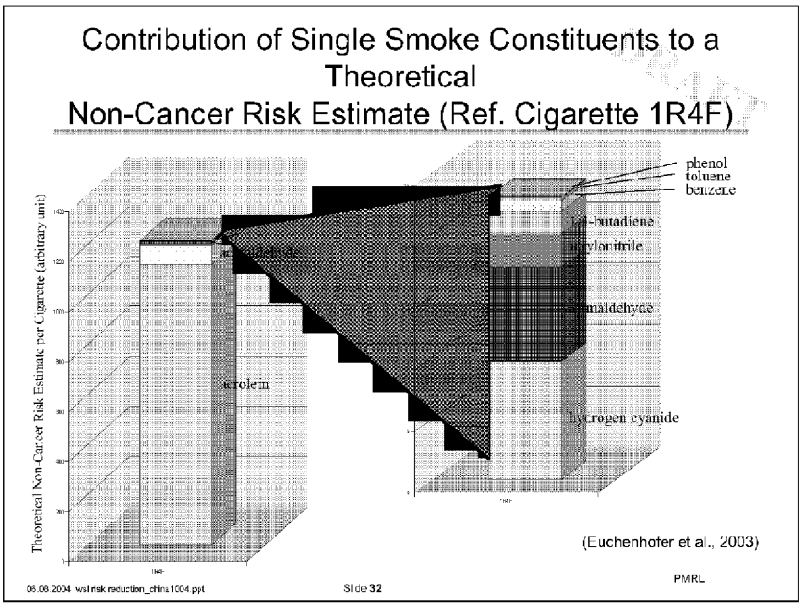

This graph illustrates the acrolein example from a theoretical risk assessment point of view. My colleague, Christian Euchenhofer, calculated the theoretical non-cancer risk for a series of smoke constituents based on the available relative potency data provided by regulatory agencies and on the amounts present in cigarette smoke. As you can see, acrolein (pink) and acetaldehyde contribute to over 90% of the relative theoretical risk for noncancer diseases for the smoke constituents measured in this approach..

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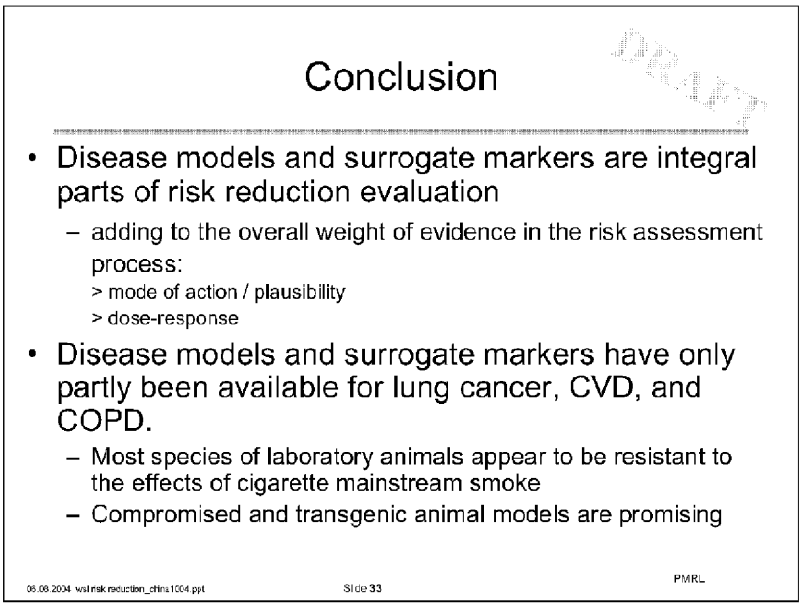

I would like to finish wish the following conclusion. As I've shown you in my examples, disease models **and** related surrogate markers are integral parts of risk reduction evaluation, and taken together, their results on the mode of action of cigarette smoke and the dose response can be woven into an overall weight-of-evidence assessment process.

I've also shown that suitable disease models and even surrogate markers have only partly been available for the three major smoking-related diseases and that we are striving to improve them. A major obstacle is the apparent resistance of the common lab animal strains to the specific cigarette smoke effects. Therefore, especially compromised or transgenic models look promising.

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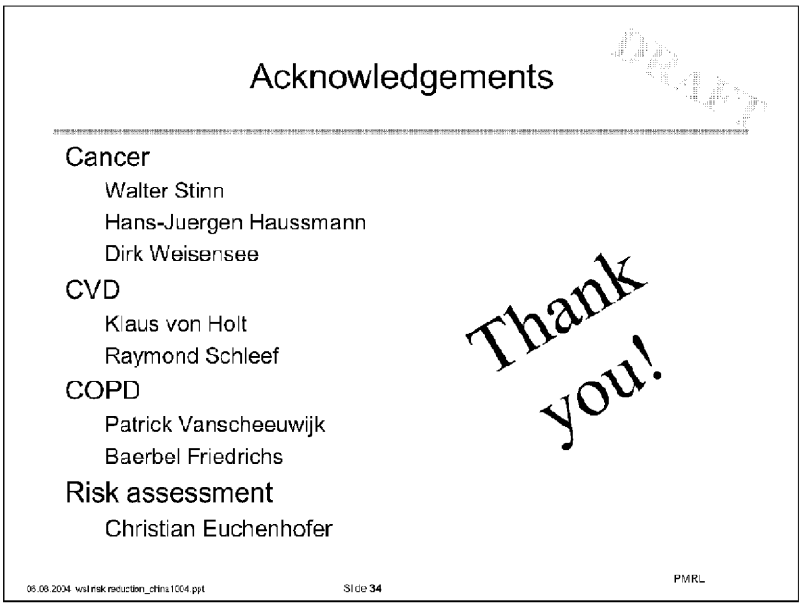

I would like to thank you all for your interest in my presentation. My special thanks to all the colleagues at PMRL who contributed to the work I was showing.

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