Appendix 2 (as supplied by the authors): Summary information on 60 documents "destroyed" by Imperial Tobacco Canada in 1992

Carcinogenicity and "Biological Activity" of Tobacco Smoke				
Document Number (hyperlinked to document)	**Document Date**	**Title and reference**	**Quotation**	**Summary**
B8	August, 1967	Long-Term Skin-Painting Experiments - Progress Report: July 1967[38]	"There is an indication from the early results that condensate produced at a low puff volume (10 ml) might give rise to more tumours than does the condensate produced at a high puff volume (50 ml)."	Progress report on the Project JANUS experiments, conducted to determine the carcinogenic components of tobacco smoke.
B11	October, 1968	The Tumorigenic Index[39]	"As already mentioned, it is quite well known that the application of smoke condensate to laboratory mice leads to death by poisoning."	A critique of Ellis' Tumorigenic Index and suggestions for improving it.
B23	September, 1971	The Promotion Activity of Tobacco Smoke Condensates to Mouse Skin B9-1 and B9-6 Cigarettes.[40]	"A comparison of the number of epithelial hyperplasias and neoplasias in condensate-treated groups with the number in acetone-treated and control animals indicates that the lesions are mainly due to the promotion activity of the tobacco smoke condensate."	This experiment demonstrated that the tumour promotion activity of tobacco tar could be quantified and measured.
RD828R	September, 1971	Retention of Nitric Oxide in the Human Respiratory System Report No:RD.828-R710921[61]	"Since, in most cases, the apparent retention of NO in the mouth was found to be comparatively low, it would seem that the disappearance of the major portion of the NO is due to events which take place lower down in the respiratory tract."	Subjects smoked cigarettes and the amount of NO retained in the respiratory system was measured. Inhaling smoke containing NO leads to a complete retention of NO unless an artificially rapid and shallow breathing pattern is employed.
RD872R	March, 1972	The First Promotion Test[29]	"…B9-1 is more active than B9-6 (a result which is in agreement with current PSR values from experiment B9) and that the higher level of DMBA increases the response."	The use of DMBA as a tumour initiator greatly increases the rate of production of tumour-bearing animals painted with B9-1 and B9-6 smoke condensate.
B28	April, 1972	Carcinogenicity of Smoke Condensate to Mouse Skin Experiment B1[43]	"The effect of increased tumorigenicity of the condensates (proportion of tumour-bearing animals) is diminished by an increased toxicity affecting life expectancy at the dose levels used. Most likely both effects are not caused by the same substances, but it cannot be excluded that toxic substances shortening life expectancy on the one hand may render animals more susceptible to tumorigenic insults on the other."	The total number of tumour-bearing animals was similar in animals treated with 25mL condensate (166) and 50mL (167) but was slightly lower in those treated with 10mL condensate (129).
B26	May, 1972	Carcinogenicity of Smoke Condensate to Mouse Skin	"Control mice had no tumours within the painted area, the number of tumour bearing animals in the	There was only a dose-response relationship of tumour-bearing mice up until 50mg of condensate for

Appendix to: Hammond D, Chaiton M, Lee A, et al. Destroyed documents: uncovering the science that Imperial Tobacco Canada sought to conceal. *CMAJ* 2009. DOI:10.1503/cmaj.080566.

		Experiment B0.[41]	condensate-treated groups was 105 (25 mg), 177 (50 mg) and 127 (75 mg)…"	the B0 cigarettes.
B27	November 1972	The Promotion Activity of Tobacco Smoke Condensates to Mouse Skin: Cigarettes B9-2, B9-3, B9-4 and B9-5[42]	"Epithelial hyperplasias and neoplasias within the painted area diagnosed by histological examination were considered to be mainly the result of the promotion activity of the various condensates."	Five experimental cigarette types were found to be tumorigenic with the incidence of skin lesions decreasing in the following order: B9-3, B9-2, B9-4, B9-5, control.
B29	September, 1973	Carcinogenicity of Smoke Condensate to Mouse Skin Experiment B2[22]	"Each of the three groups originally included 252 animals. The number of tumour-bearing animals in the condensate-treated groups was 85 (25 mg), 180 (50 mg), and 182 (75 mg)."	All 3 doses of cigarette B2 were found to be tumorigenic with a dose-response relationship being present from 25mg to 50mg where the number of tumour-bearing animals increased by more than 100%.
B30	March, 1974	Experimental Tumorigenesis in the Hamster Larynx The Promoting Activity of Inhaled Smoke from Cigarette BO[44]	"From this pilot study it appears that tobacco smoke may act as a promoter in laryngeal carcinogenesis."	Pre-treated hamsters exposed to cigarette smoke were more likely to develop lesions in the larynx and pharynx
B31	March, 1974	Carcinogenicity Of Smoke Condensate To Mouse Skin Experiment B3[45]	"Each of the three groups originally included 252 animals. The number of tumour-bearing animals in the condensate-treated group was 31 (25 mg), 124 (50 mg) and 157 (75 mg), considering only tumours which did not regress permanently."	Three doses (25, 50, and 75mg) of cigarette B3 were found to be tumorigenic with a significant dose-response relationship from 25mg to 50mg exposure groups with the number of tumour-bearing animals increasing fourfold from 25mg to 50mg.
B32	September, 1974	Carcinogenicity Of Smoke Condensate To Mouse Skin Experiment B4[46]	"From this it appears that with the dose range between 25 and 50 mg a pronounced dose effect was observed but that the 75 mg dose was too high for this type of condensate. These results correspond with those found in Experiments B0 and B3."	Cigarette condensate B4 was found to be tumorigenic at all 3 doses of 25, 50, and 75 mg with a significant dose-response relationship from 25 to 50 mg.
RD1198R	April 14, , 1975	The design and analysis of an experiment to compare the tumour-promoting activities of the condensate from cigarettes D184 to D189 inclusive[60]	"Summarising the results of these significance tests, we have that the six condensate treated groups of animals produced significantly more tumour-bearing animals than the control group, but these condensate treated groups were not significantly different among themselves."	All six experimental groups had more tumours than the control group, but the experimental groups were not significantly different from each other.
B33	April, 1975	Carcinogenicity of Smoke Condensate to Mouse Skin Experiment B5[47]	"A comparison of number and incidence of initial tumours in the original and the repeated condensate groups (B5) shows agreement with regard to condensate B2 and B3; however the number and incidence of initial tumours were lower (147 versus 176'' 63 percent versus 74 percent) in the repeated experiment with respect to the B0 condensate."	A repeat of Janus experiments B16, B29, and B31. All cigarette types were again found to be tumorigenic.

Appendix to: Hammond D, Chaiton M, Lee A, et al. Destroyed documents: uncovering the science that Imperial Tobacco Canada sought to conceal. *CMAJ* 2009. DOI:10.1503/cmaj.080566.

B34 RD1212R (Statistical analysis of experiment B34, attached as appendix to B34[22])	January, 1976	Carcinogenicity of Smoke Condensate to Mouse Skin Experiments B6 and B7.[48]	"The high mortality was obviously due to the toxic effect of the condensate treatment since it was dose-dependent without exception."	Tumorigenic activity of i) condensates produced from two different cigarettes, and ii) condensates produced from various levels of cuts per inch during the manufacture of cigarettes were observed on mice. It was found that increasing the cuts per inch on cigarettes reduced the malignant tumorigenicity of condensates.
B35 RD1180R (Statistical analysis of experiment B35, attached as appendix to B35[21])	March, 1976	The Promotion Activity of Tobacco Smoke Condensate to Mouse Skin: Cigarettes B11/1, B11/2 and B11/3.[49]	"The two groups of animals receiving the condensate from the control blend and the Type B Reconstituted Tobacco produced significantly more tumour-bearing animals than the control group receiving no condensate treatment."	The incidence of animals with lesions was lowest in the control group and for the 3 cigarette types, the incidence of lesions were as follows: B11-2 (24%), B11-1 (23%), B11-3 (17%).
RD1352R	April, 1976	A Statistical Analysis of the Incidence of Tumour-Bearing Animals in Janus Experiment B8.[32]	"The special filter significantly increases the tumorigenic activity of the condensate. Even after allowance has been made for the reduction in TPM caused by the filter, the tumorigenic activity on a per cigarette basis is still higher for the filter cigarette than for the unfiltered version."	The experiment showed that the use of a silica gel filter to produce the condensate reduced the condensate's toxicity, but increased its tumorigenicity.
B37	June, 1976	Experimental Tumorigenesis in the Hamster Larynx. The Activity of Inhaled Smoke from Cigarette B 12/1 and B12/2.[50]	"Of the 264 hamsters exposed to smoke, 15 had grade 4 lesions (5.7%), while this type of lesion occurred only in one of the 108 animals (0.9%) that had not inhaled cigarette smoke…The six fold increase in the number of grade 4 lesions demonstrates a tumour-enhancing effect of inhaled cigarette smoke."	Hamsters were exposed to smoke from two different cigarettes to measure tumorigenicity. Exposure to smoke resulted in a six fold increase in the number of grade 4 laryngeal lesions and smoke exposure had a dose-dependent effect.
RD1394U	July, 1976	A Review of the Genetics and Consequences of Alpha 1-Antitrypsin Deficiency Report No. RD. 1394-U. Unclassified[62]	"...cigarette smoke produces changes which are believed to precede emphysema, and that it contains substances which are independently associated with emphysema. In fact patients with emphysema who have never smoked are rare, and in Pi phenotypes ZZ the available evidence suggests that smoking hastens the onset of the disease. It would appear that smoking acts as a "trigger" for emphysema, particularly in Pi ZZ phenotypes that are pre-disposed to the disease".	This paper reviewed the available literature on α1-antitrypsin deficiency, its relationship with cigarette smoking and its association with the occurrence of emphysema. The evidence suggests that cigarette smoke triggers the onset of emphysema and it also contains substances which are independently associated with emphysema.
AT090	September, 1976	Review of Biological Testing Methods[23]	"Although associations have been drawn between smoking and a number of diseases, these are strongest in the case of lung cancer, bronchitis, emphysema, cardiovascular disease, and low birth weight in infants."	A review of the available tests and methods for measuring the health effects of cigarette smoke. Tests for tumorigenicity have been developed; however, no tests for other conditions associated with smoking, such as cardiovascular disease, are available.

Appendix to: Hammond D, Chaiton M, Lee A, et al. Destroyed documents: uncovering the science that Imperial Tobacco Canada sought to conceal. *CMAJ* 2009. DOI:10.1503/cmaj.080566.

B39	September, 1976	A Study on the Tumour Promoting Activity of Tobacco Smoke Condensates Applied to Mouse Skin: Cigarettes B13/1 - 8.[51]	"Although in this laboratory, data for long-term skin painting are unavailable it is reasonable to assume that most of these tumours were caused by the promoting activity of condensate. The tumorigenic effect of the initiator alone was obviously slight."	After week 14, there was a positive dose-response relationship with the dose of the cigarette condensate of all cigarettes types and the incidence of tumour-bearing animals.
B40	November, 1976	Experimental Tumorigenesis in the Hamster Larynx The Effect of Inhaled Smoke from Cigarette B0 on Vitamin-A Deficient Animals.[52]	"The data suggest that vitamin A deficiency had an enhancing effect on the progression of lesions caused by inhaled smoke and that this effect was more pronounced at the lower smoke level."	Hamsters deficient in vitamin A were exposed to cigarette smoke to measure tumorigenicity in the form of laryngeal lesions. A dose-dependent effect of smoke inhalation was found.
B41	March, 1977	Carcinogenicity of Smoke Condensate to Mouse Skin Experiment B8.[53]	"A pronounced dose effect can be seen with all condensates, even though the animals died earlier in the higher dose groups."	Summary: The tumorigenicity of condensates from cigarettes with two different smoking materials as well as the addition of a special filter were examined in mice. The special filter increased the tumorigenicity of the condensate while tumorigenicity remained unchanged with the use of smoking material B and decreased with smoking material A.
B42	April, 1977	The Promotion Activity Of Tobacco Smoke Condensate To Mouse Skin, Dose Dependence And Interaction Of Dmba B9/1 And B9/6 Condensates.[54]	"B9/1 groups treated with 20 mg condensate had 24 mice (38 percent) affected while the treatment with 80 mg B9/6 condensate resulted in 22 mice (35 percent) affected, which indicates that the B9/1 condensate was about four times as active as the B9/6 condensate."	The tumorigenicity of cigarette condensates was measured in mice, using epithelial hyperplasias and neoplasias as the indicators of tumorigenicity. A dose-response relationship was found for B9/1 condensate from 20 mg to 40 mg and for B9/6, there was a dose-dependent effect from 40 mg to 80 mg
RD1394A	April, 1977	"A Review of the Genetics and Consequences of Alpha 1-Antitrypsin Deficiency Report No. RD. 1394-A. Unclassified"[63]	"…Cigarette smoke produces marked changes in the alveolar macrophages of both human and animal lungs. A comparison of the alveolar macrophages obtained from healthy smokers and non-smokers by pulmonary lavage has shown that smokers have many more macrophages than non smokers…."	This document reviewed the available literature on α1-antitrypsin deficiency, its relationship with cigarette smoking and its association with the occurrence of emphysema.
B43	July, 1977	A Study on the Tumour Promoting Activity of Tobacco Smoke Condensates Applied to Mouse Skin: Cigarettes B32/1-6.[55]	"Tumour promoting activity was demonstrated for all condensates tested by their occurrence rates of TBA in excess of that for the corresponding acetone control group. The TBA percentage for the condensate categories varied from 20.0% (B32/6) to 33.3% (B32/4) compared with 10.8% for the same number of mice treated with acetone."	The tumorigenicity of 6 cigarette condensates (5 experimental, 1 control) was measured in mice. Tumour promoting activity was found to be greater in all experimental groups compared to the control group.
B44	August, 1977	A Statistical Analysis of the Incidence of Tumour-Bearing Animals in Janus Promotion Study B30/31 Report No. RD.1517	"The analysis of a more complex Battelle promotion study has shown that pretreatments of 120 µg or 180 µg of DMBA give subsequent tumour rates which are not significantly different..."	Both B9/3 and B9/5 cigarette condensates were found to be tumorigenic. As well, control tobacco was more tumorigenic than reconstituted sheet tobacco (PRT) variants and this was significant when PRT was manufactured at higher base levels.

Appendix to: Hammond D, Chaiton M, Lee A, et al. Destroyed documents: uncovering the science that Imperial Tobacco Canada sought to conceal. *CMAJ* 2009. DOI:10.1503/cmaj.080566.

		Restricted.[34]		
B45	October, 1977	A Comparison Of The Tumorigenic Activities Of Janus Condensates B0, B2 B4.[35]	"From the comparison of B0 and B4 it is clear that reducing the stem content of the blend leads to an increase in tumorigenic activity, and from the analysis of the N.C.I. data it can be seen that the inclusion of Burley tobacco in the blend leads to an increase in activity."	A statistical re-analysis of some earlier experiments of Project Janus found that the addition of Burley and stems in cigarettes leads to an increase in tumorigenic activity and the use of cocoa, sugar, and/or humectants has no effect on tumorigenic activity.
B46 RD1481R (A Statistical Analysis of the Incidence of Tumour-Bearing Animals in Janus Experiment B9[49])	October, 1977	Carcinogenicity of Smoke Condensate to Mouse Skin Experiment B9.[56]	"A comparison of the results shows that the tumorigenic activity of the condensates decreases in the sequence B9/1, B9/3, B9/2, B9/4, B9/5, B9/6. The differences between groups are quite pronounced except between groups B9/2 and B9/4 where it is small."	The tumorigenicity of condensates produced from cigarettes using various methods of tobacco manufacture were measured on mice. The control blend (conventional manufacture method) had higher tumorigenic activity than cigarettes with extracted tobacco, cigarettes with the tobacco extract returned, and cigarettes with 3 different types of reconstituted sheet materials.
B49	March, 1978	Carcinogenicity of Smoke Condensate to Mouse Skin Experiment B10.[57]	"Dose dependence was observed for all five condensates regarding the occurrence and incidence of tumours if the 28.3 mg, 40 mg, and 56.6 mg dose groups are considered."	The tumorigenicity of condensates produced from 5 types of cigarettes containing different materials (1 control, 4 experimental) were observed in mice. The 3 cigarettes containing substitute materials were more tumorigenic than the control cigarette, with cigarettes with a higher % of substitute A being more tumorigenic than those with a lower %. Cigarettes with reconstituted sheet material were less tumorigenic than all other groups.
B50	March, 1978	Carcinogenicity Of Smoke Condensate To Mouse Skin, Experiment B11.[58]	The tumorigenic potency of the condensates, expressed by the average number of tumours related to the total number of animals per dose group, increases from cigarette B11/3 to B11/2 and then to B11/1, and is clearly dose dependent in all groups…"	Summary: The tumorigenicity of condensates produced from 3 types of cigarettes (1 control, 2 types of 100% reconstituted tobacco) were observed in mice. It was found that all 3 types were tumorigenic and the tumorigenic activity of reconstituted tobacco type B was markedly lower compared to the control group.
RD1729C	March, 1980	A Comparative Inhalation Study on Smoke From Cigarettes with Different Filters Report No. RD.1729-C.[66]	"Three points arise: i) Reduction of suspected irritants may not necessarily lead to a reduction in the specific biological activity of whole smoke. ii) Smoker reaction to changes in smoke chemistry may have an important bearing on whether such changes produce a real improvement in a cigarette from a smoking-and-health standpoint. iii) A 'league table' approach to improving cigarette smoke characteristics may be misleading in the absence of back-up evidence from toxicity and/or smoking	The inhalation toxicity of cigarettes with 4 different types of filters (1 cellulose acetate/paper filter, 3 different types of vapour phase filters) was examined in rats. It was found that vapour phase filter cigarettes produced the most severe lesions in the respiratory system compared to the control filter cigarettes (which was the opposite of what was expected). Dosimetry results show that this is due to an increased deposition of TPM.

			behaviour studies."	
T153C	October, 1984	Ames Mutagenic Activity of Mainstream Condensate of Six Commercial Cigarettes for Imperial Tobacco Ltd (Canada) Project Rio: Report No. T153-C Restricted.[21]	"...with a 1.3-fold difference between the maximum and minimum activities. However, with the possible exception of Craven A and PLAYERS LIGHT, the differences in specific activities are so small that the cigarette series should be considered as having similar activities."	Six brands of Canadian cigarettes were all found to be mutagenic. Their ranking on the Ames test from highest to lowest was: 1. Craven A, 2. Players Light, 3. DuMaurier, 4. Export A, 5. Mark Ten, 6. Matinée.
T169	January, 1987	Ames Mutagenic Activity of Sidestream Condensate of Eight Commercial Cigarettes from the Finnish Market.[36]	"It can be seen that there is no marked difference in the shape of the dose-response curves between the cigarette with the most mutagenic activity (40A) and that of the least (H)."	Eight Finnish brands and both prototype cigarettes were found to be mutagenic with the most mutagenic cigarette being 1.39 times more mutagenic than the least mutagenic cigarette (based on relative specific activity).
T172	January, 1987	Ames Mutagenic Activity of Sidestream Condensate. Comparison of Prototype Slim Cigarettes & Six Commercial Cigarettes from the Swiss Market.[37]	"...the slim cigarette with acetate paper (V533) was 32% more active than the corresponding product with conventional paper (v532) and 72% more active than the lowest commercial product (cigarette A). The remaining 5 commercial cigarettes had a range of activities between these products."	Six Swiss brands and both prototype cigarettes were found to be mutagenic with the most mutagenic cigarette being 1.91 times more mutagenic than the least mutagenic cigarette (based on relative specific activity)
RD808R	November, 1995	Analysis of Janus Condensate Solutions.[28]	"…Hoffman and Wynder have recently reported that "tar" with doubled and tripled concentrations of seventeen aromatic polycyclic hydrocarbons demonstrates increased tumorigenicity."	Preliminary study of chemical analysis of tobacco smoke condensate for its carcinogenic potential. Rather than benzo[a]pyrene, tar, with higher concentrations of seventeen polycyclic hydrocarbons was found to be a better predictor of tumorigenicity.
FE026	Unavailable	Biological Activity of Cigarette Smoke and Condensate: Results of Biological Investigations. (Translation from German)[59]	"To determine the biological activity of tobacco smoke, one must look at the cause-effect relationship of the complex smoke, splitting into the components of active agents (active principles), kinds of activity (kinds of tissue) and mode of activity (stimulation, acute irritation, irreversible damage)."	An analysis of biological tests for analysing tobacco smoke or tobacco smoke condensate. It is generally assumed that cigarettes modified to have lower biological activity and the largest possible number of test organisms is more favourable for the smoker.
Second-hand Smoke				
RD1519R	August, 1977	Changes in the Respiratory Tract of Rats Exposed to Smoke for 5 or 7 Days Per Week for 6 Weeks Report No. RD.1519.[73]	"All values in smoke-exposed groups were greater than their corresponding controls. The changes in the lung parenchyma and bronchi were all greater in those animals exposed to the higher concentration of smoke."	The lung pathology of rats that were exposed to smoke for 5 and 7 days per week, for 6 weeks, was examined. All smoke-exposed animals had greater development of lesions in lung, trachea, and larynx compared to the control group.

Appendix to: Hammond D, Chaiton M, Lee A, et al. Destroyed documents: uncovering the science that Imperial Tobacco Canada sought to conceal. *CMAJ* 2009. DOI:10.1503/cmaj.080566.

RD1552R	December, 1977	Scanning Electron Microscope Study of the Response of the Larynx and Trachea of the Rat to Smoke Exposure Report No. RD. 1552 Restricted.[74]	"In general terms, the size of the response of the larynx to smoke (as determined by measuring squamous epithelial width at a specific site) was rapid at first and similar for all smoke concentrations. Subsequent exposures for up to 3 weeks at the 3 highest concentrations produced a further increase but at different rates."	Groups of rats were exposed for up to 3 weeks to 4 different concentrations of smoke. It was found that in all exposed rats, there was a consistent smoke-induced change in the larynx. There was a dose-response relationship after 3 weeks for rats exposed to the 3 highest concentrations of smoke.
RD1553R	December, 1977	Response of the Rat Larynx and Trachea to Smoke During Smoke Acclimatisation Period Report No. RD. 1553 Restricte[d.75]	"As indicated by previous studies, smoke-induced changes in the rat larynx occurred after a relatively short-term exposure to dilute smoke…In this study, minor changes were seen after only 2 days of acclimatisation schedule and continued exposure increased the response of the larynx to smoke."	Groups of rats were exposed to 2 dilutions of cigarette smoke for a maximum of 8 days, including a 1st day of full smoke exposure, to observe changes in the respiratory tract, particularly the larynx. Evidence of squamous hyperplasia became evident after 5 and 8 days of exposure and keratinisation was more prominent in rats exposed to higher concentrations of smoke.
RD1566R	March, 1978	Distribution of Inhaled Smoke Particles in the Rat Lung Report No. RD.1566 Restricted.[26]	"Again, we have demonstrated that a larger proportion of TPM retained by rats during smoke exposures is trapped in the lungs. With regard to the proportional distribution of TPM, at the higher smoke concentration we again observed an increase proportion of TPM deposited in the head."	Rats were exposed to cigarette smoke and the distribution of smoke particulate matter was measured in their lungs. A clear relation to exposure level was found and a dosage gradient of particulate matter in the lung lobes was found, with the highest dosage being found in the right superior lobe.
RD1589R	May, 1978	Studies on Mucus Production(First Report) Report No.RD1589 Restricted.[76]	"…repeated chemical stimulation results in the production of a less sulphated mucus. These results largely agree with our findings that the degree of sulphation of the mucus glycoproteins decreases in response to increasing levels of (chemical irritation) smoke exposure."	Tracheal mucus production in rats exposed to cigarette smoke were assessed. After 8 weeks an increase in total tracheal mucus production and a decrease in sulphated tracheal mucus production was found.
RD1633R	November, 1978	Pilot Long-Term Inhalation Study (Interim Report) Report No. RD.1633 Restricted.[27]	"Exposure of animals to smoke for up to 52 weeks has shown a clear progression of the smoke-induced lesions in the lower respiratory tract and a maintenance (slight progression?) of those observed in the larynx."	The respiratory system of rats that were exposed to cigarette smoke for a period of 52 weeks was observed. The condition of the respiratory system was greatly reduced after being exposed to smoke as smoke-induced lesions were found in the lower respiratory tract and mucus-producing goblet cell activity was reduced.

Appendix to: Hammond D, Chaiton M, Lee A, et al. Destroyed documents: uncovering the science that Imperial Tobacco Canada sought to conceal. *CMAJ* 2009. DOI:10.1503/cmaj.080566.

RD1640R	December, 1978	Acute Physiological and Biochemical Measurements in Response to Whole Smoke, Vapour Phase and Pure CO Exposure Report No. RD. 1640 Restricted.[77]	"The respiratory rates of animals exposed to pure CO compared with those obtained from animals exposed to equivalent concentrations of CO from whole smoke and vapour phase were markedly different. The respiratory rates of animals exposed to whole smoke or vapour phase were less than 50% of the rates obtained from animals exposed to equivalent concentrations of CO."	The physiological and biochemical effects in rats after being exposed to smoke were observed. The researchers also attempted to isolate the role of CO and nicotine in mediating these changes. It was found that smoke and some of its constituent parts interact and disrupt basic metabolic pathways.
RD1734R	May, 1980	Investigation of Sidestream Smoke Constituents From Four Tobacco Types Report No. RD1734.[72]	"It would seem that the amounts of semi-volatile nitrogenous components, especially pyridines and pyrazines, is higher in the sidestream smoke than in mainstream. Especially for low delivery cigarettes, this suggests that it is the "passive smoker" who obtains the larger amounts of these components, albeit in a diluted form, rather than the smoker himself."	A comparison of the components of mainstream and sidestream smoke found that semi-volatile nitrogenous compounds (ex. Pyridines) and nicotine were found to be higher in sidestream smoke which means that it's the "passive" smoker who intakes larger amounts of these chemicals.
RD1747C	June, 1980	An Exposure System for the Bioassay of Inhaled Sidestream Cigarette Smoke Report No. RD.1747-C Restricted.[78]	"In the trachea, particularly in the group exposed to smoke for 4 x 1 hour/day, there was a marked deciliation of the lining epithelium and a loss of mucus producing goblet cells. At the level examined (the section included the parathyroids and thyroids) the ciliated cells were often replaced by transitional epithelium which in 3 rats had progressed to a focal squamous metaplasia. Tracheal lesions of this severity have not been observed in our previous mainstream studies including those of much longer duration."	The pathological and physiological changes in rats exposed to sidestream smoke were observed. The respiratory rate decreased and the changes to the larynx and lungs were similar to the changes seen in rats exposed to mainstream smoke.
RD1921R	April, 1983	Characterisation of the Conditions Necessary for a Sidestream Smoke Inhalation Bioassay Report No. RD.1921 Restricted.[79]	"Shorter periods are useful in illustrating the pathogenesis of the epithelial changes but are not sufficient to produce the desired fully differentiated hyperplastic and metaplastic changes regarded as "end point" lesions. Even with 4 days exposure bronchial lesions still include foci of necrosis."	The researchers examined the conditions necessary, including exposure regime and duration, to produce significant changes in the respiratory tract of rats when exposed to sidestream smoke.
RD1922R	May, 1983	The Way in which Air Ionizers Reduce the Density of Smoke in a Closed Environment.[80]	"The estimated effective reduction in the exposure which might be experienced by a subject varied between 19% and 46% in five different rooms, and in general terms could be considered to be less than 40%. This effect could easily be overwhelmed by increased ventilation obtained, for example, by opening a window."	The study examined the effectiveness of air ionizers in removing sidestream smoke. The finding was the air ionizers do remove tobacco smoke, however, it wasn't found to be any more effective than simply opening a window or door.
Nicotine Addiction and Compensation				
RD953R	November, 1972	Preparation and Properties of Nicotine Analogues Report	"Should nicotine become less attractive to smokers, the future of the tobacco industry would become less	Scientists made several attempts to synthesize analogues of nicotine, however, they were

		No RD.953-R.[69]	secure." "It has been suggested that a considerable proportion of smokers depend on the pharmacological action of nicotine for their motivation to continue smoking. If this view is correct, the present scale of the tobacco industry is largely dependent on the intensity and nature of the pharmacological action of nicotine. A commercial threat would arise if either an alternative product became acceptable or the effect of nicotine was changed."	unsuccessful.
RD1300R	January, 1976	Compensation for Changed Delivery Report No. RD. 1300. Restricted.[24]	"From the foregoing discussion the evidence is strongly in support of the hypothesis that many smokers do change the way they smoke in response to cigarette design changes that affect nicotine delivery…The tendency amongst the majority of established smokers is to attempt to equalise nicotine delivery if the cigarette design allows them to do so."	A review of evidence regarding the change in smoking patterns amongst smokers in response to changes in cigarette design and delivery. It was found that many smokers do compensate for changed delivery in an attempt to equalise nicotine delivery.
RD1632R	November, 1978	Triple Filters Containing Mixed Adsorbents Report No. RD.1632[65]	"These observations suggested that possibly the magnesium silicate has a high affinity for the rapid adsorption of Total Volatile Aldehydes but lacked the ability to retain them. Lewatit E372/74, whilst not adsorbing the aldehydes as rapidly as magnesium silicate, has the capacity to combine substantially irreversibly with the aldehydes thus removing them permanently from the mainstream smoke vapour phase."	Different mixtures of components in cigarette filters were tested for their effectiveness on filtration performance and filtration efficiency for Total Volatile Aldehydes and hydrogen cyanide. The mixture of ion exchange resin and porous magnesium silicate was found to be the most advantageous since it was lower in cost, didn't contain carbon, and it had similar filtration efficiency to other mixtures.
RD1652R	March, 1979	Dr. MAH Russell's "Safer Cigarettes" Study Report No RD 1652.[71]	"Some smokers, in fact, felt giddy while smoking the cigarette, presumably because they used the mouth sensations as cues to estimate their smoke intake. As a result of taking sufficient smoke to cause acceptable mouth sensations they would receive nearly twice as much nicotine as usual, resulting in the feeling of giddiness. This suggests that the texture of the smoke in future designs of low tar to nicotine ratio cigarettes must be improved."	Smokers were asked to smoke 3 cigarettes, their own brand, a control cigarette, and one of two experimental cigarettes (a low-nicotine cigarette or a cigarette with a low tar to nicotine ratio). When blood samples were taken it was found that those who smoked the lower delivery cigarette had lower blood plasma nicotine levels and lower carboxyhaemoglobin levels compared to their own brand while those who smoked the low tar to nicotine ratio cigarettes had higher levels blood plasma nicotine and carboxyhaemoglobin levels compared to their own brand.
RD1789R	March, 1981	Examination of a Concept Proposed by Gori for Rating Cigarettes.[70]	"The concept cannot be communicated effectively through conventional brand advertising. Statements relating to 'safety' in smoking would have severe legal implications. Even with the removal of such constraints, it was clear that smokers would still be highly sceptical regarding any claims made by the manufacturer."	Consumer research was conducted on Dr. Gori's "critical levels" of cigarette smoke exposure. Although smokers expressed interest in the idea, particularly low tar cigarette smokers, the researchers noted that smokers would be highly sceptical of a manufacturer's claim and they would require a third party endorsement from an authoritative, independent, and

				objective body.
RD1960R	March, 1984	Receptors for Nicotine in the Central Nervous System Report Number RD 1960.[25]	"...it is apparent that the binding of nicotine is not simply to one binding site since displacement by several compounds shows a marked biphasic nature. This indicates that these compounds displace nicotine from two distinct binding sites, the affinities of the compounds for the sites being non-identical."	This paper examined how nicotine from cigarette smoke interacts with receptors in the brain. It was found there are at least two binding sites, one high-affinity nicotine-cholinergic site and one low affinity non-nicotine-cholinergic site.
Tobacco Additives				
RD391R	November, 1966	The Transfer of Flavouring Materials Part I Coumarin From Pipe Tobacco Report No. Rd. 391-R.[15]	"The results show that the transfer of coumarin is between 63% and 69% and a similar transfer value (64%) was found for a sample of "Amphora", Full Aromatic (Douwe Egberts) tobacco containing 0.09% coumarin. In the present experiments the transfer of coumarin was some 6 – 8% higher than the transfer of nicotine."	The amount of coumarin transferred to mainstream smoke when smoking coumarin-impregnated pipe tobacco was examined. The amount transferred was found to be slightly higher than the amount of nicotine transferred.
RD402R	May, 1966	The Transfer of Flavouring Materials Part II - 6-Methylcoumarin from Pipe Tobacco.[16]	"The results show that the transfer of 6-methylcoumarin from pipe tobacco is very similar to that found for coumarin (63-69%). Like coumarin, the transfer of 6-methylcoumarin from this tobacco is somewhat higher than that of nicotine."	Two alternatives to coumarin, 6-Methylcoumarin and dihydrocoumarin, were examined to compare the amount transferred to mainstream smoke. The amount of 6-Methylcoumarin transferred was found to be similar to coumarin and the amount of dihydrocoumarin could not be detected in the smoke.
RD505R	September, 1967	The Transfer of Coumarin: Part III – The Transfer from Pipes and Cigarettes Under Various Smoking conditions and the Retention of Coumarin by Smokers Report No. Rd.505-R.[17]	"The absorption of coumarin in the human has also been measured using a small panel of smokers. It was found that virtually all (more than 95%) of the coumarin is retained when the smoke is inhaled. The level of retention is probably less than 10% if the smoke is not inhaled."	The amount of coumarin transferred to smoke when smoking under standard conditions was examined. It was found that an increase in puffs per minute did not significantly affect the amount of coumarin transferred. As well, virtually all the coumarin is retained when the smoke is inhaled compared to less than 10% if the smoke is not inhaled.

Appendix to: Hammond D, Chaiton M, Lee A, et al. Destroyed documents: uncovering the science that Imperial Tobacco Canada sought to conceal. *CMAJ* 2009. DOI:10.1503/cmaj.080566.