

AN ALTERNATIVE STRATEGY OF RISK REDUCTION FOR TOBACCO SMOKERS



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CURRENT STRATEGIES OF RISK REDUCTION FOR TOBACCO SMOKERS



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- **1st strategy: Ceilings on suspected toxic compounds**
 - WHO Study Group on Tobacco Product Regulation, 2008.
 - «Non-exhaustive priority list of tobacco and smoke constituents».
- **2nd strategy: Nicotine reduction to address addiction**
 - WHO Study Group on Tobacco Product Regulation, 2015.
 - «The maximum nicotine content should be as low as is technically feasible».

Can we imagine an alternative strategy of risk reduction for tobacco smokers?



1st STRATEGY: CEILINGS ON SUSPECTED TOXIC COMPOUNDS



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The list of tobacco contents and emissions of cigarette smoke was defined by WHO on the basis of the following criteria:

- the presence of specific chemicals in cigarette smoke at levels that are toxic for smokers as determined by scientific toxicity indices;
- variations in concentrations among cigarette brands that are substantially greater than the variation in repeated measurements of the toxicant in a single brand;
- the existence of technological routes to mitigate these yields.



ARE THERE CONSTITUENTS THAT CAN BE REDUCED BY DEVELOPPING NEW TOBACCO PLANT ?



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- Many constituents in tobacco and tobacco smoke are influenced by the genetics of the tobacco plant.
- Molecular markers to identify and follow these genes could be used in traditional breeding in order to develop new plants.



- Necessity to identify the **links between gene variability and chemical variability** observed in tobacco and/or in tobacco smoke using the IMB seeds collection and the **genetic association methodology**.

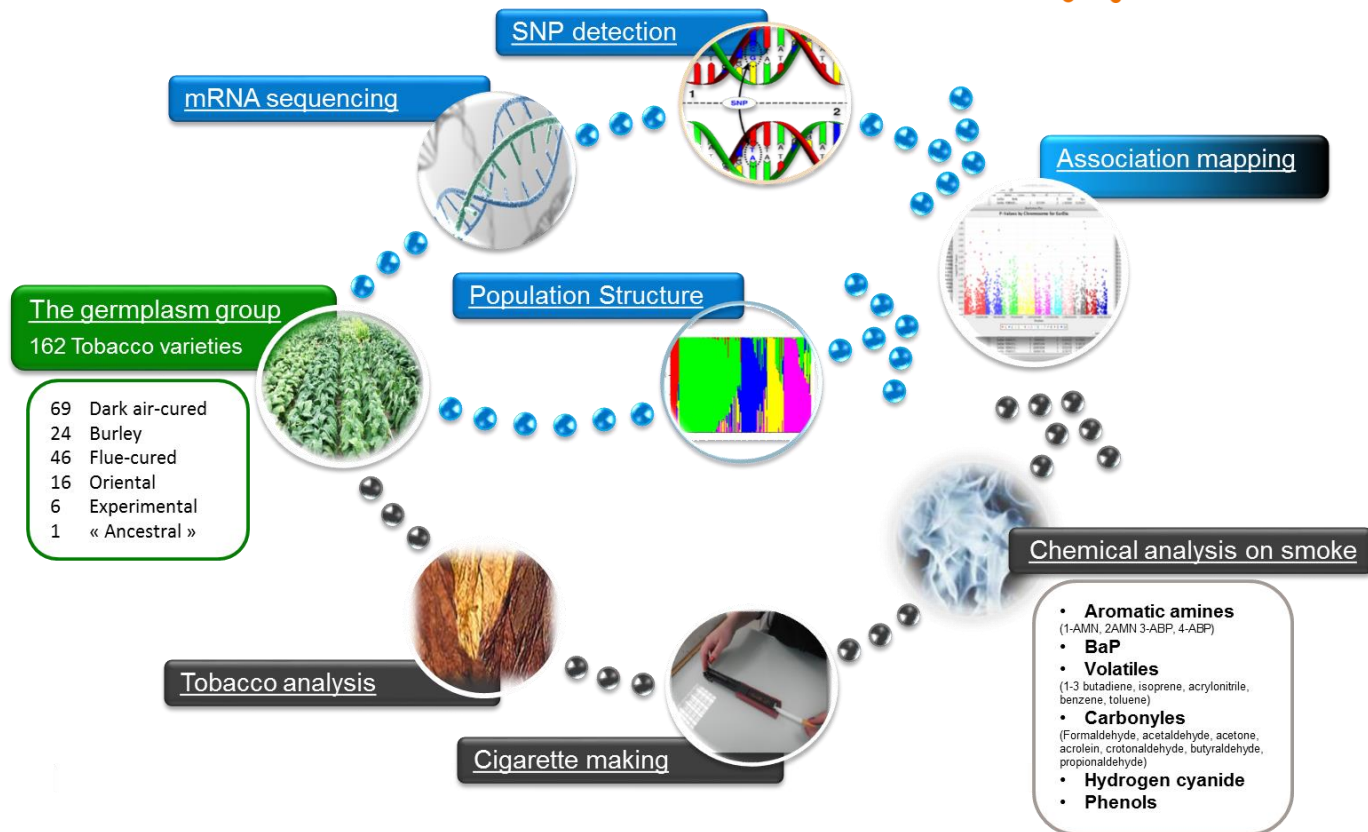


GENETIC ASSOCIATION METHODOLOGY



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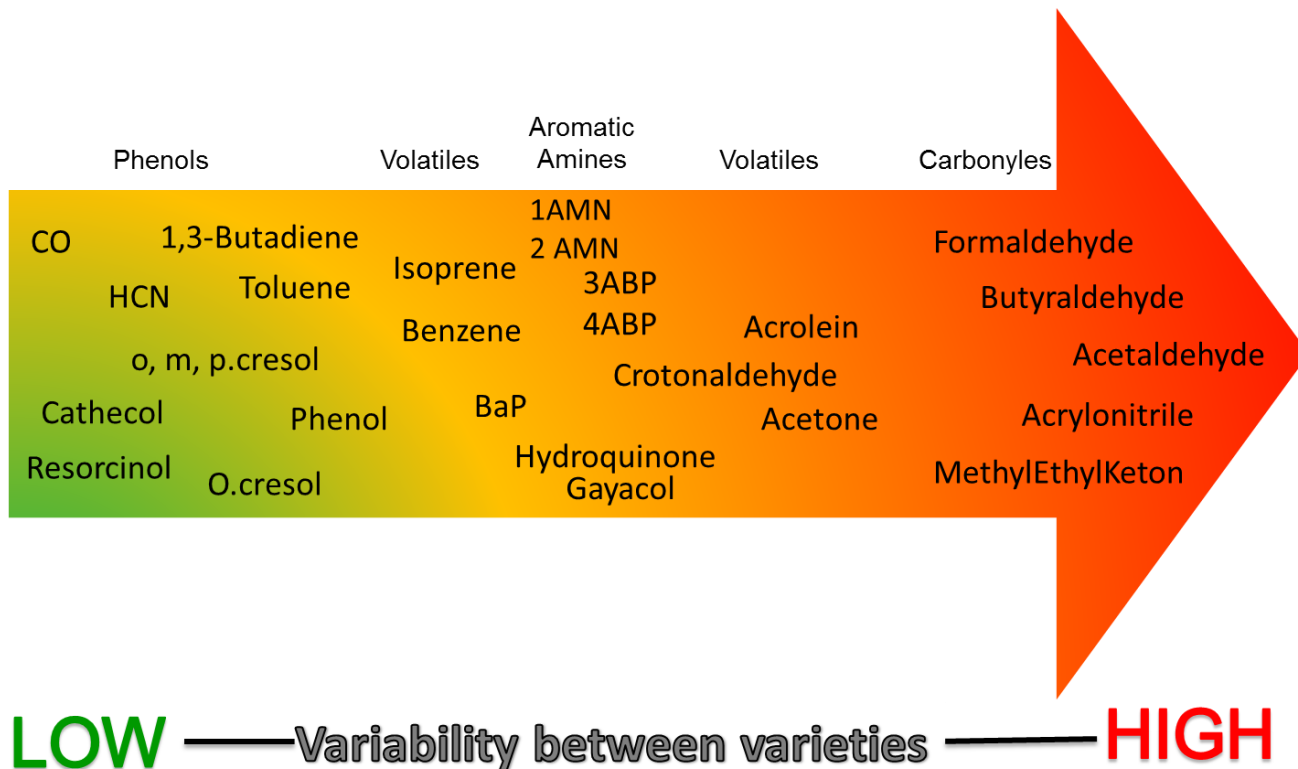


VARIABILITY OF SMOKE CONSTITUANTS



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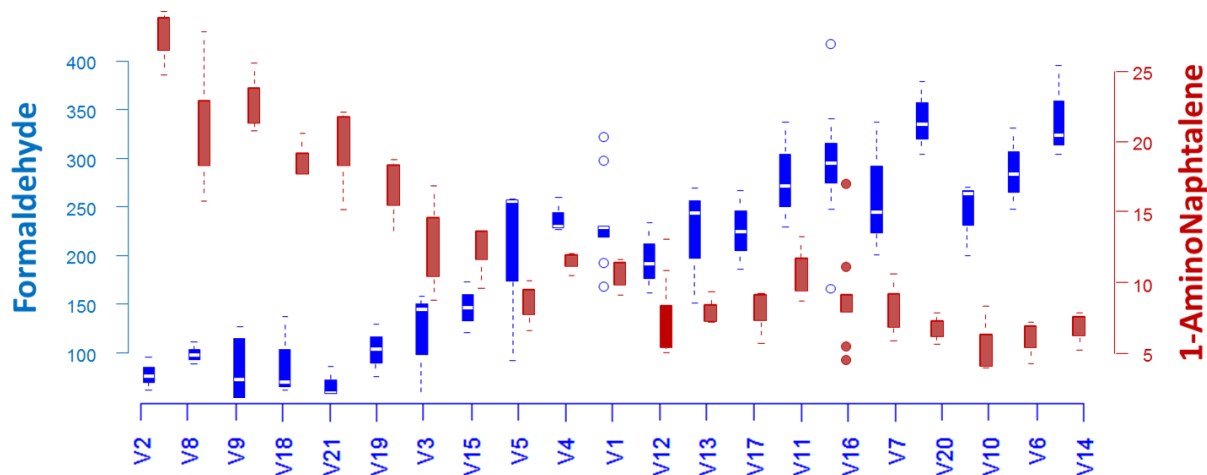


NEGATIVE CORRELATIONS



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- In some cases lowering the yield of one smoke constituent may result in increasing the yield of another.
- Nitrogen oxides and amino- or nitroso-aromatic compounds negatively correlate to formaldehyde and acrolein, or benzo(a)pyrene and di-hydroxybenzenes.





- **Pro**
 - Almost 7000 SNPs were identified in *Nicotiana tabacum* genes.
- **Cons**
 - No real evidence about the involvement of these compounds in toxicity of tobacco products.
 - Difficulties to achieve a large number of chemical analysis and repeats on tobacco smoke.
 - Negative correlations between some compounds.
 - No variability for other compounds.
- **This strategy is hard to implement practically but some targets like TSNAs can be treated individually by mutagenesis of nicotine demethylase.**



2nd STRATEGY: NICOTINE REDUCTION TO ADDRESS ADDICTION



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WHO AND FDA POSITIONS

- Tobreg (WHO), October 2015: *“The maximum nicotine content should be as low as is technically feasible. At present, that level would appear to be 0.4mg nicotine per gram of cigarette tobacco filler”*. That means **0.04% in raw tobacco**.
- *“Addressing the addictive levels of nicotine in combustible cigarettes must be part of the FDA’s strategy for addressing the devastating, addiction crisis that is threatening American families”* said Scott Gottlieb, the FDA commissioner, July 2017.
- *“FDA is particularly interested in comments about the merits of nicotine levels like 0.3, 0.4, and 0.5mg nicotine/g of tobacco filler, as well as other levels of nicotine”*, March 2018. That means **0.03 to 0.05% in raw tobacco**.



POSSIBLE SOLUTIONS, PROS AND CONS



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Solutions	Reduction	Pros	Cons
Cultivars selection and cultural practices	-50% (LN)	Varieties available, Easy to implement, (5 to 7 years minimum).	CPA application increase, Low yield (Trials ongoing), Taste change, acceptability by smokers?
Conventional breeding and cultural practices	-80 to 90% (VLN)	Technically feasible, (10 to 12 years minimum).	CPA application increase, Low yield, Taste change.
Extraction	Up to -80%? (VLN)	Technology available, (10 to 12 years minimum).	Cost (factories), Destructive, product is different → processing issues, Taste change & residues, or not industrially feasible.
Biotechnologies	-98 to 99% (ULN)	Technically feasible, (10 years minimum without authorizations).	Patents on genes and technology, Regulatory authorization needed, Public opinion is anti-GMO in Europe, Impact on trading, CPA application increase, Yield?, Bad quality, Practicability unknown .





- Low Nicotine (50% reduction) is feasible and practical: with a 5-7 year program, 1% nicotine in leaf could be achieved.
- However, lowering nicotine may undermine sustainability and prove counterproductive: significant risk of increased illicit trade (T. Verron *et al.*, CORESTA, 2017 and 2018).
- Feasibility is not the same as practicability.

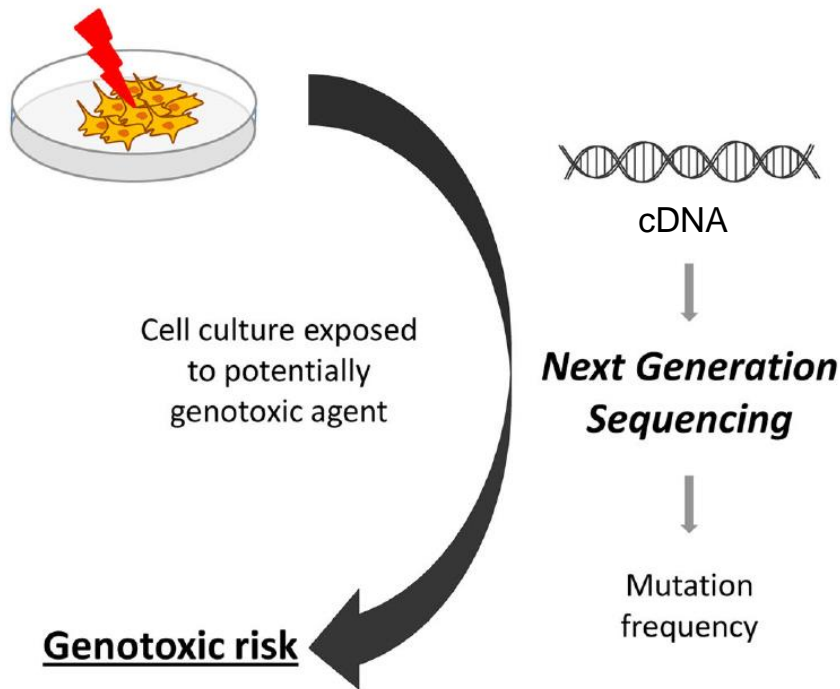


AN ALTERNATIVE STRATEGY BY TOXICOTRANSCRIPTOMICS?



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Maslov et al., 2015

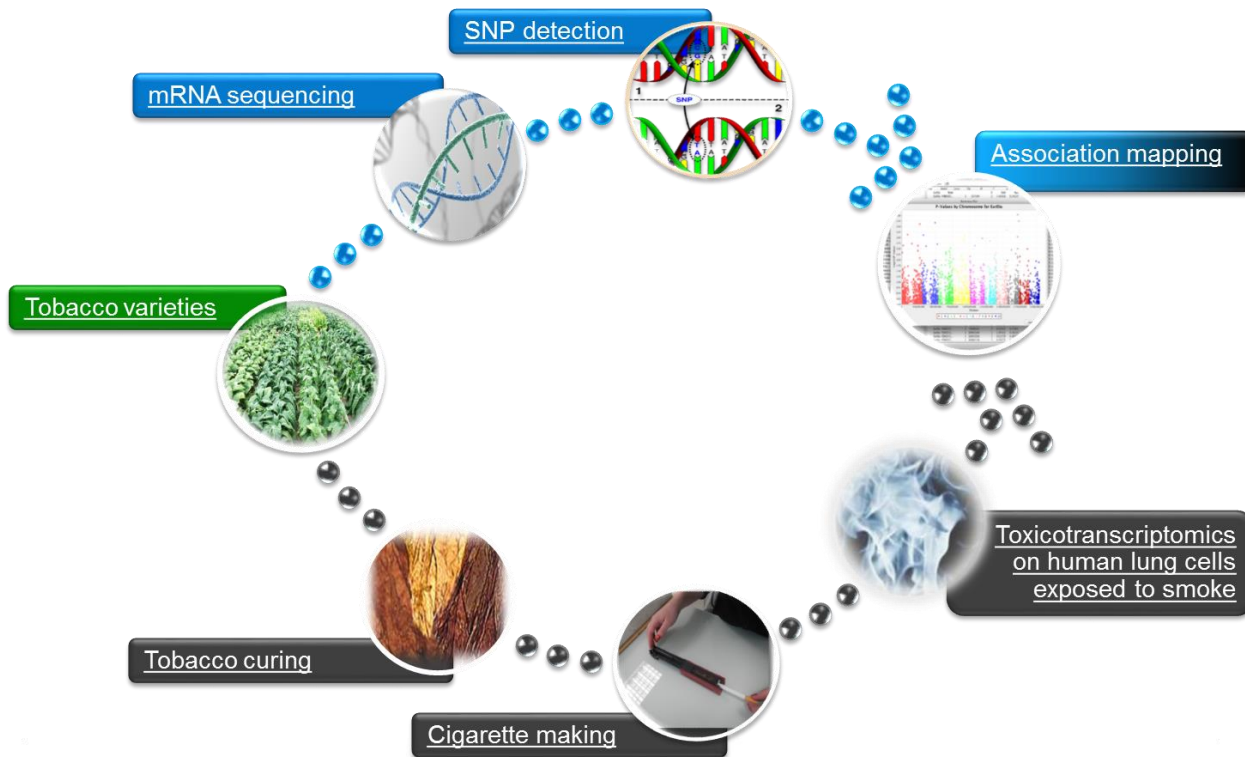


PLANT MOLECULAR MARKERS ASSOCIATED TO TOXICITY ON HUMAN CELLS



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A STRATEGY BASED ON TOXICOTRANSCRIPTOMICS, WHY?



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- SNPs on *Nicotiana tabacum* can be obtained easily.
- For cost and practical reasons, work only on the Human transcriptome:
 - on specific targets (genotoxic risk or expression);
 - or on the whole transcriptome and global assessment of the genotoxic risk.
- That strategy is practically easier and quicker to develop than the first strategy based on specific chemical compounds analysis.





- Without knowing the true causes of the toxicity of tobacco products, we can now hope to identify molecular markers associated with this toxicity.
- The development of new tobacco varieties could significantly reduce the impact on the smoker.



TO SUM UP



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1. The multi-ceilings strategy is practically not possible to implement. But a chemical target like TSNAs can be decreased significantly by mutagenesis of nicotine demethylase.
2. The Low Nicotine reduction (50%) is feasible and practical: with a 5-7 year program, 1% nicotine in leaf could be achieved. However, an impact on illicit trade can be feared.
3. The high throughput sequencing paved the way to new perspectives in term of risk reduction for smokers. Studies based of natural variants of tobacco associated with an assessment of smoke toxicity by transcriptomics could lead to the development of new relevant tobacco cultivars.





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Thank you.

