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Strategy for Toxicity Evaluation of Tobacco Additives and their Regulation

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REGULATION OF TOBACCO ADDITIVES*

Most chemical products such as industrial chemicals, pharmaceuticals, pesticides or food additives are subject to strict regulation in the European Union in order to protect public health. The products have to be tested for their safety before they are authorized for use. They must be fully characterized in various short- and long-term tests, in particular with regard to their potential organ toxicity, carcinogenicity, mutagenicity, reproductive toxicity and allergenicity. The results of the testing are evaluated by the regulatory authorities and the substance is approved or rejected on the basis of the assessment process. Up to now, tobacco additives are exempted from this procedure. This anomaly has been addressed in the EU Directive 2001/37/EC on the regulation of tobacco products [1].

The Directive stipulates in Article 6 that manufacturers and importers of tobacco products submit a list of all ingredients and quantities thereof, used in the manufacture of tobacco products, to the member states. The reasons for the inclusion of such ingredients in the tobacco products should be stated. The list must also be accompanied by the toxicological data available on the additives in burnt or unburnt form as appropriate. Finally, in Article 11, the Directive calls for paying special attention to "methodologies for more realistically assessing and regulating toxic exposure and harm" [1].

The provisions of the Directive have not been implemented throughout the EU including Germany [2, 3]. Neither has a systematic collection and evaluation of the toxicological data of tobacco additives been made, nor a strategy been developed for assessing and – if required – toxicological testing and evaluating potentially toxic tobacco additives.

* Footnote: The term "additives" corresponds to the term "ingredients" used in EU Directive 2001/37/EC. The Directive is not entirely consistent in its use of the term "ingredients", in that it applies the term also to tar, nicotine and carbon monoxide (Article 6, point 3) and uses both this term and the term "additives" inconsistently in the preamble.

FEATURES OF TOBACCO ADDITIVES

Depending on the country, tobacco product manufacturers are permitted to add any of about 600 agents to their products [4]. The added materials may account for up to 20 percent of the total weight of a cigarette. The agents serve various purposes. They are used as humectants, flavours, preservatives, solvents and binders. They help to standardize tobacco brand products and to cover up poor taste of inferior-quality tobacco. Furthermore, they reinforce the smoker's preference of a specific tobacco product by their pharmacological and sensory action potential.

The agents that are authorized as tobacco additives in Germany [5] and other EU states have originally been classified as food additives and were considered to be safe as such. The uncritical equalization of tobacco additives with food additives dates back more than 40 years. In view of the current state of knowledge, this equalization is no longer acceptable. It is apparent that the toxicological characterization and evaluation of tobacco additives must substantially differ from that of food additives. The reasons for this are twofold:

1. Additives may be harmless when ingested orally with food. But this may not be the case if they are inhaled in tobacco smoke. Inhaled substances come in contact with the large inner surface of the lungs, where they may act as irritants or suppressors of irritation. For example, glycerol or sorbic acid are well tolerated when ingested with wine, but they may irritate the respiratory tract when inhaled. Moreover, many substances are absorbed faster and more efficiently through the lungs than through the gastrointestinal tract.

2. In the burning cigarette, tobacco additives are subjected to high temperatures and converted into multiple new substances [6–8], called pyrolysis products and pyrosynthesis products (in the following referred to as „pyrolysis products"). Many of these products have been identified and evaluated as being toxic and carcinogenic [8].

Clearly, tobacco additives have to be subjected to toxicological assessment which takes into account their specific mode of application. This must include an assessment of their inhalation toxicity in their burned and unburned form as well as the toxicological evaluation of the pyrolysis products which are formed in the heat of the burning zone (600–900° C).

This communication presents a proposal for the toxicological assessment of tobacco additives and their pyrolysis products based on the aforementioned considerations.

CONCEPT OF A TOXICITY TESTING AND EVALUATION PROCEDURE

The following outlines the basic principles of the proposed concept for the toxicity testing and evaluation of tobacco additives and of the regulatory consequences.

Basic Principles

The present concept is based on the principles of preventive, regulatory toxicology.

Proof of safety

The procedure is aimed at characterizing and evaluating the hazard of the additives in burned and unburned form.

Additives in tobacco products have no health value. On the contrary, by making smoking more attractive, they promote a behaviour which is extremely unhealthy (see below). In consequence, the level of proof of safety must be set very high and regulatory measures be strictly enforced. Here, the precautionary principle as a quintessential element of preventive toxicology should come into full force [9]. It stipulates that a reasonable suspicion of toxicity is sufficient to deny approval of such a substance. For example, not only substances recognized as carcinogens must be banned from use, but also substances suspected to be carcinogenic.

Assessment of individual substances

Following established toxicological procedures, the test substances must be characterized and evaluated as single agents. Mixtures of substances derived from natural products such as oils of roses,

liquorice or honey, may be subjected to the same testing procedure as single substances.

Tier system
The evaluation and toxicological testing should be carried out in a multi-step tier system (see Figure 1). This involves a decision tree where the results of one step determine the actions of the next step. Such a procedure helps to considerably reduce the efforts spent in time, energy and costs.

Use of existing knowledge
Whenever possible, information already available on the toxicity of the test substance should be used and evaluated before new analytical-chemical or biological tests are initiated. There exists, in fact, broad knowledge on the toxicity of many tobacco additives as well as on the identity and toxicity of their major pyrolysis products.

Burden of proof
The burden of prove for the safety of tobacco additives lies with the manufacturer/importer of tobacco products. The regulatory authorities evaluate the submitted documents on the additives and grant or refuse approval as they do with other chemical substances to be marketed e.g. industrial chemicals, pesticides or drugs. Tobacco additives differ from these substances only in that their toxicity has to be assessed in unburned and burned form.

Steps of the tier system

Step 1
Toxicological evaluation of additives in their unburned form
This step is required because some of the tobacco additives which had been approved as safe in the 1970s are now known to be toxic or carcinogenic [8, 10, 11]. Examples are glyoxal, azo dyes, chromium complex colours and talc. Moreover, as noted above, the toxicity of a substance may greatly differ depending on the route of application. Many tobacco additives are not completely converted to pyrolytic products, but pass partly unchanged from the burning zone of the cigarette to reach the lower airways. This requires a case by case assessment, to determine whether and to which extent the toxicity of the test substance differs when ingested via the gastrointestinal tract or the airway system. Toxicological testing of additives in their unburnt form should only be carried out, if the available data are insufficient for the required evaluation (see also step 4).

Step 2
Toxicological evaluation of pyrolysis products
The major pyrolysis products of many tobacco additives have been identified and their toxicity has been described [7, 8, 10, 12, 13]. This information can be directly used for the toxicological assessment and evaluation, provided the experimental conditions for pyrolyzing the additive (e.g. temperature, oxygen concentration) were sufficiently realistic.

Step 3
Pyrolysis of additives and toxicological evaluation of the products
If the pyrolysis products of an additive are not known, the additive has to be pyrolyzed as a single agent under realistic and standardized conditions. The pyrolysis products should be identified with the most sensitive methods of analytical chemistry. Based on the results, a toxicological evaluation of each individual pyrolysis product should be made using published data (as in steps 1 and 2).

At present, no generally accepted method for a realistic and standardized pyrolysis of tobacco products is available. Critical parameters that influence the outcome of the pyrolysis are the temperature and oxygen concentration in the burning zone. The authors suggest that an institution which is independent of the tobacco industry develops a standard for the pyrolysis of tobacco products. In the meantime, published test results which were obtained under reasonably realistic pyrolysis conditions may be used for the evaluation process.

Step 4
Toxicological testing of additives or their pyrolysis products
If the information available in steps 1 to 3 is insufficient for the evaluation of the additives and pyrolysis products, they must be tested for their toxicity. The

testing should follow validated, internationally recognized procedures such as those set by guidelines of the OECD (e.g. guideline 471; bacterial mutation test or guideline 451; long-term carcinogenicity testing) or of the International Conference on Harmonization of Pharmaceuticals.

Implementation, evaluation and regulatory implications

The toxicity testing should follow the common practice of internal and external quality control. It should be dimensioned at the various steps to result in clear conclusions on the safety of the test substance. A toxicological risk evaluation for the tobacco additive is made at the end of each step.

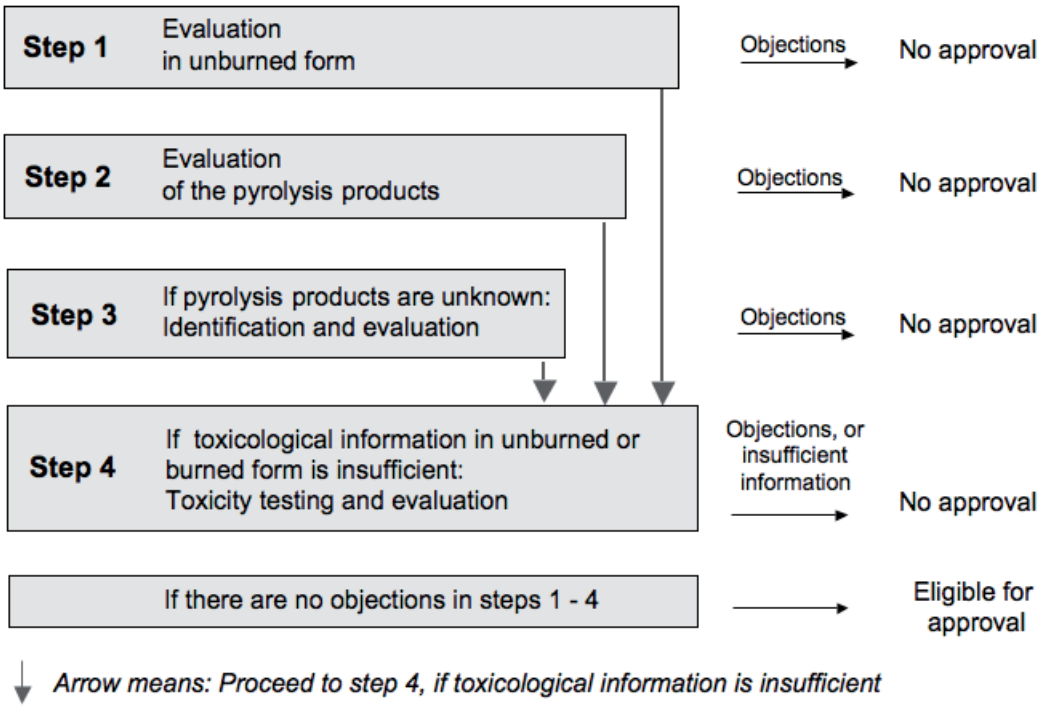
If any of the steps yields an indication that the additive or one of its pyrolysis products is carcinogenic, mutagenic or teratogenic, it can not be approved. Substances exhibiting other toxic effects may be eligible for approval provided they are taken up in amounts too small to pose a significant risk.

DISCUSSION

Alternative, tobacco industry-favoured strategy for toxicity assessment

The concept of testing and evaluating tobacco additives proposed here is fundamentally different from the approach recommended by the tobacco industry [14]. The latter stipulates that the toxicity of the additive should not be tested per se, i.e. independently of the tobacco product. Rather, the additives should be admixed to the tobacco product and the tobacco smoke analyzed for changes in the degree of toxicity [15].

Tier system for toxicological evaluation of tobacco additives and their regulation



This approach is unsuitable to prove the safety of an additive for a number of reasons: The analytical-chemical detection methods currently available may not be sensitive enough to detect all the potentially toxic pyrolysis products or quantify them with sufficient accuracy due to the high background of thousands of pyrolysis products generated from the tobacco itself. The biological and toxicological testing of the tobacco smoke is even more problematic. The many highly cytotoxic ingredients of tobacco smoke would render it impossible to properly assess the genotoxicity of the additive e.g. in an in vitro test.

Overall, the procedure proposed by the tobacco industry implies that the additive may be as toxic as the pyrolysis products of the tobacco. In practice, only if the additive increases the toxicity of the tobacco smoke, will it be banned. Finally, this approach would make it unfeasible to regulate additives in a consistent manner. Given that tobacco products differ in their basal toxicities, the relative additional toxicity of the additive would differ from tobacco product to tobacco product. Under such conditions, the establishment of a standard positive list of tobacco additives is virtually impossible.

In principle, the norm of the safety of additives can never be derived from the toxicity and carcinogenicity of the product itself. There is no reason why tobacco products should be exempted from this principle.

Further need for toxicological testing

Substances affecting the pyrolysis pattern of a tobacco product

Tobacco additives which are employed to modulate the combustion and condensation behavior of tobacco, such as metal compounds, cannot be tested using the proposed methods. In this case, the substance may be added to the tobacco product and its effect on the components of the mainstream and sidestream smoke analyzed. Since presently no standardized methods for testing the toxicity of the entire tobacco smoke are available – and are not likely to be available in the near future, – testing of modulators of combustion and condensation is not feasible for the time being.

Residues

The term "tobacco ingredients" is more broadly defined by the WHO Study Group on Tobacco Product Regulation (TobReg) than by the directives of the EU. According to the WHO study group, ingredients include all product components, materials used to manufacture those components, residual substances from agricultural practices, storage and processing, and substances that can migrate from package material into the product [16].

Residues of concern are, in particular, the pesticides applied during cultivation of the tobacco plant and tobacco storage. Several hundred pesticides are used in tobacco cultivation and processing worldwide. If their residues are not subject to regulatory controls, (e.g. by threshold limit values), their toxicity should be assessed using the testing procedure presented here. This is advisable, because the pesticides, too, may be more toxic when taken up by inhalation than by oral ingestion and their pyrolysis products may exhibit an unforeseen toxic profile.

In a broader view, residues include substances which get into the tobacco plant due to special cultivation methods. For example, fertilization with sewage sludge increases the uptake of carcinogenic ions of cadmium, arsenic, lead, chromium, nickel or cobalt into the tobacco plant [17]. Also, fertilization with nitrates increases the nitrate content in tobacco plants and, thus, leads to increased pyrolytic conversion of organic compounds to highly carcinogenic nitroso- and nitro-products. Such changes in the consistence of the tobacco and tobacco smoke elude the testing and regulation procedure proposed here. They may be limited by setting threshold levels for toxic ingredients of the tobacco plant/material itself and its smoke. The establishment of guidance values and threshold levels for a number of these ingredients is on the way.

Need for regulation of other harmful properties of tobacco additives

Addictive effects

The EU Directive 2001/37/EC calls for the establishment of a common list of tobacco additives "which takes into account inter alia their addictiveness". Prominent representatives of such additives are

pH-modulating substances. For example, ammonium compounds and other alkaline substances, such as the amino acid lysine, are added to release ammonia [18]. Ammonia, in turn, converts nicotine from its ionized form into its non-ionized form which is much faster absorbed by the smoker than the ionized substance providing him with a nicotine boost soon after inhalation of the tobacco smoke [18]. The addiction-enhancing effect of tobacco additives is not subject matter of the present testing procedure. So far, no informative methods are available to test such effects [19]. They will have to be regulated separately from the toxic effects of additives.

Other pharmacological effects

Apart from potentially enhancing the addictiveness of tobacco products, additives or their pyrolysis products may have multiple pharmacological and neurophysiological effects [20]. Substances such as menthol, which is added to some brands of cigarettes in high amounts, alleviate irritation and have cooling and anesthetic effects. Other substances such as theobromine dilate the airways and facilitate deeper inhalation of the tobacco smoke. The relevance of these effects on smoking behavior and tobacco dependency is unclear. Documents of the tobacco industry reveal that the substances under consideration are added to promote the consumption of tobacco products. This should be reason enough to deny their approval as tobacco additives. Substances with pharmacological-neurophysiological effects can hardly be differentiated from those which alter the organoleptic properties of tobacco products.

Enhanced attractiveness of tobacco products

The majority of additives is used to make tobacco products more attractive to the consumers. They are added as individual substances, e.g. sugar and ethylvanillin, or as mixtures, e.g. liquorice, honey, syrups, molasses, fruit extracts and oils, to improve the taste of tobacco products or to mitigate the unpleasant, harsh tobacco flavor. For example, the cigarette factory of British American Tobacco in Bayreuth has been reported to process about 400 tons of honey per year [21]. Furthermore, the additives help to standardize the products and thus contribute to the brand loyalty of consumers. By providing a milder taste, they make it easier for children, teenagers and adults to start smoking.

Overall, the increase in tobacco consumption due to the taste-improving features of additives is likely to cause more harm than their toxicity. Thus, there is a long-standing call for banning all additives which increase the attractiveness of tobacco products. Recently, the U.S. has taken legal steps to prohibit all synthetic and natural flavorings – other than menthol – for use in tobacco products [22]. Hopefully, the EU will follow this example.

SUMMARY

Most of the tobacco additives currently used are converted to potentially organ-toxic, mutagenic, carcinogenic or teratogenic products during pyrolysis in the smoldering tobacco product. So far, no officially recognized testing strategy exists that enables the evaluation of additives for their safety in unburned and burned form. The present proposal wants to close the gap.

The proposed testing and evaluation procedure is in accordance with the principles and practice of regulatory preventive toxicology:

1. The central aim of the procedure is to assess the **proof of safety**.

2. The **burden of proof of safety** lies with the manufacturers and importers of tobacco products.

3. The testing and evaluation has to be carried out on **individual substances**, i.e. the single additive and its pyrolysis products.

4. The substance should be tested and evaluated in a **tier system**.

5. The testing should utilize **internationally accepted and validated methods**. A standardized procedure must be developed for the pyrolysis of the test substance reflecting the chemical

and physical conditions in the heat zone of the tobacco product as closely as possible.

6. The evaluation will resort to the **available toxicological information** on the test substance.

7. A substance which gives **reason of concern** in any of the testing and evaluation steps will not be approved.

The proposed toxicological assessment of tobacco additives and their regulation represents only minimum measures for consumer protection. From a larger perspective, all substances which increase the attractiveness and the consumption of tobacco products should be banned in the interest of public health.

Finally, trying to protect against harmful tobacco additives, it should be kept in mind that the tobacco products themselves - with and without additives - cause millionfold disease, disability and death. Therefore, any conceivable measure should be taken to eliminate tobacco from the market - as quickly as possible.

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