Bundesministerium
Soziales, Gesundheit, Pflege
und Konsumentenschutz

AGES

Guideline

for

the evaluation of Heated Tobacco Products

regarding their health impact

in comparison to cigarettes based on

emission measurements and toxicological studies

1. Legal Framework

Pursuant to § 10a TNRSG, an authorisation from the Federal Ministry of Health (BMSGPK) is required for the marketing of novel tobacco products. The Office for Tobacco Coordination is the assessment body within the framework of this authorisation process (NTZulV).

On behalf of the BMSGPK, the Office for Tobacco Coordination, in cooperation with the Department for Risk Assessment, has developed a strategy for evaluating heated tobacco products (novel tobacco products) with regard to their health effects compared to cigarettes.

Based on § 3 para. 2 line 1 NTZulV this guideline for the evaluation of heated tobacco products was created.

Pursuant to § 10a para. 4 TNRSG, authorisation is to be granted if the relevant applicable regulations for the novel tobacco product in question are complied with. If several variants of a product are requested for authorisation with one application, each variant is considered a product to be authorised separately.

The word "available" in § 10a para. 2 line 3 to 5 TNRSG is (also) with regard to § 10a para. 3, 2nd sentence TNRSG, not to be understood in the sense of studies that happen to be in the possession of the respective applicant, but all the studies according to the state of the art for the respective question that can/must be commissioned and are necessary for the assessment of the product. The documents to be submitted in accordance with § 10a para. 2 line 3 to 5 TNRSG must therefore at least comply in scope and quality with the requirements of the guidelines according to § 3 para. 2 line 1 and 3 NTZulV in order to enable a state of the art examination and assessment.

In the interest of ensuring public health and consumer protection, an authorisation is only to be granted if there are no indications found, that the product, which is subject to authorisation, could have more harmful effects than a comparable conventional product.

The prerequisite for authorisation is therefore that the information/data specified in section 5 of this guideline

- **is submitted for each individual product that is subject of the application**
- **is submitted in full to the assessment body and**
- **give no indication that the product subject to authorisation could have more harmful effects than a comparable conventional product.**

2. Heated Tobacco Products

are novel tobacco products that are heated with a device to produce emissions containing nicotine and other chemicals that are consumed by inhalation.

3. Strategy for Evaluating Heated Tobacco Products

AGES is not aware of any strategy for assessing the health effects of heated tobacco products that has previously been recommended or followed by other competent assessment bodies or other scientific bodies.

Therefore, on behalf of the BMSGPK AGES has developed its own internal strategy according to the state of the art in science and technology, to compare the health effects of heated tobacco products with those of cigarettes.

From a toxicological point of view, the route of exposure of harmful substances, i.e. trough ingestion, through the skin or through inhalation, is a decisive factor for the magnitude of caused health effects.

Since the way of consumption of heated tobacco products, i.e. the inhalation of a nicotine-containing aerosol, resembles the consumption of cigarettes, the comparison with cigarettes occurs to be reasonable from a toxicological point of view.

4. Health Effects of Cigarettes and Expectable Data Availability regarding Health Effects of Heated Tobacco Products

Smoking damages almost every organ and causes, amongst others, cancer, cardiovascular disease, chronic obstructive pulmonary disease, other lung diseases and diabetes. Furthermore, it increases the risk of a number of other diseases such as tuberculosis, specific eye diseases, immunological diseases including rheumatoid arthritis (CDC , DKFZ).

Some diseases only appear after years or decades of cigarette consumption, such as the development of various types of cancer.

These long-term effects in humans can only be demonstrated by long-term studies. Therefore long-term studies would be required to examine long-term effects of heated tobacco products. However, since heated tobacco products have only been available on the market and therefore have been consumed for a very short time, such studies are usually not available.

In vivo animal experiments are also suitable to investigate on long-term effects and provide valuable information on whether similar effects are also possible in humans. Animal experiments could be used to assess long-term health effects of heated tobacco products. However, in the interest of animal welfare and in compliance with the European Directive 2010/63/EU on the protection of animals used for scientific purposes, the opinion is expressed that testing heated tobacco products on animals should be avoided as far as possible. For the assessment of health effects of heated tobacco products, it should therefore be assumed that no animal studies are available.

Consequently, it is to be expected that a health assessment of heated tobacco products can only be carried out to a very limited extent and only on the basis of *in vitro* toxicological studies or chemical/analytical data on specific product properties.

In this regard, it is pointed out that a comprehensive assessment of the health effects of heated tobacco products is therefore not possible. Any long-term effects or effects that are not toxicologically measurable *in vitro* cannot be evaluated.

5. Minimum Requirements on Data and Information for the Assessment of Health Effects of Heated Tobacco Products

To ensure reliability on the validity of the data, internationally recognized test procedures should be used as the basis for a health assessment of heated tobacco products. In addition, it should be ensured that the tests used as a basis for assessment were carried out properly and to a statistically robust extent.

From AGES´s perspective, the following information should be used for a health assessment of heated tobacco products:

A. Emissions
   - of parameters/substances according to the WHO priority list
   - Further information on emissions that are decisive for a health assessment due to specific product designs or certain ingredients. These must be adapted to the respective product properties. For example, in the case of heated tobacco products that contain components with metals (e.g. an aluminium casing) or that come into contact with metal components when used (e.g. a heating plate), emissions of the corresponding metals must also be taken into account.

B. *in vitro* toxicological studies
   - cytotoxicity test
   - bacterial reverse mutation test
   - *in vitro* mammalian cell gene mutation or micronucleus test

It is expressly stated that an assessment based on this data in no way represents a comprehensive assessment of the health effects of the products. The data/studies according to points A and B only offer statements regarding the measured end points and no further conclusions can be made about emissions and toxicity of the heated tobacco products.

Long-term consequences of consuming the products cannot be estimated. Even if the information according to sections A and B indicate lower toxicity of heated tobacco products compared to cigarettes, this does not rule out the possibility that similar harmful effects to health as from cigarettes also emanate from heated tobacco products.

Likewise, other potential, as yet unknown, health consequences of consuming heated tobacco products cannot be assessed and therefore cannot be ruled out.

5.1 Detailed Description of the Required Data as Basis for Assessment

A) Emissions

According to the currently valid ISO standard 8243, samples of heated tobacco products must be taken in all factories at a certain point in time. The data set must consist of at least 5 different batches.
→ Detailed information on the sampling carried out (place, time, number of samples, batch numbers) must be made available.

The data set to be transmitted must contain measured emission values for the parameters specified in List A of the individual product compared to the measured emission values of these parameters for the reference cigarette 3R4F (or 1R6F) as follows:

- as actual values of emissions per stick
- as values relative to the nicotine content in the emissions

For both units of the values (per stick and per mg of nicotine in the emissions), at least the following information must be provided:

- Mean
- Standard Deviation
- Number of batches/samples of the product that were measured independently (n)
- Comparative presentation of the values of the product and the standard cigarette 3R4F (or 1R6F) with regard to the REDUCTION or INCREASE of emissions of individual parameters in %, including statistical evaluations of these.
- Limit of Quantification for each individual parameter (only for values per stick)

List A: Minimum required emission measurement parameters for the health assessment of a heated tobacco product.

Alkaloids	Nicotine
Aldehydes	Acetaldehyde
	Acrolein
	Butyraldehyde
	Crotonaldehyde
	Formaldehyde
	Propionaldehyde
Aromatic Amines	1-Aminonaphthalene
	2-Aminonaphthalene
	3-Aminobiphenyl
	4-Aminobiphenyl
Hydrocarbons	1,3-Butadiene
	Benzene
	Isoprene
	Toluene
PAH	Benzo[a]pyrene
TSNA	N'-Nitrosonornicotine (NNN)
	Nicotine-derived nitrosamine ketone (NNK)
	N- Nitrosoanabasine (NAB)
	N- Nitrosoanatabine (NAT)
Phenols	Catechol
	m-Cresol
	p-Cresol
	o-Cresol
	Phenol
	Hydroquinone
	Resorcinol
Other organic compounds	Acetone
	Acrylonitrile
	Quinoline
	Pyridine
Metals und metalloids	Arsenic
	Cadmium
	Lead
	Mercury
	product specific metals[1)]
Other	Ammonia

	CO
	Hydrogen cyanide
	Nitric oxide
	Nitric dioxide
	"Tar" (nicotine-free dry particulate matter, NFDPM) [2)]
	product specific Emissions [3)]

1) not included in WHO priority list. For products that contain components with metals (e.g. an aluminium casing) or that come into contact with metal components (e.g. a heating plate) during use. Emission measurements for all metals contained are required for a health assessment.
2) not included in WHO priority list. According to §10a para. 2 line 2 in connection with § 8 TNRSG emission measurements for tar, nicotine and carbon monoxide are to be transmitted.
3) not included in WHO priority list. Emissions that are decisive for a health assessment due to specific product designs or certain ingredients are required.

B) *in vitro* toxicological studies

B1) *in vitro* cytotoxicity tests (complying with Health Canada Guideline T - 502 (HC 2004b))

B2) Bacterial Reverse Mutation Test (complying with OECD Test No. 471 and Health Canada Guideline T-501 (HC 2004a, OECD 2020))

B3) *in vitro* Mammalian Cell Gene Mutation or Micronucleus Test (complying with OECD Test No. 476, 490 or 487 and Health Canada Guideline T-503 regarding the sampling (HC 2004c, OECD 2016a, OECD 2016c, OECD 2016b))

The following criteria must be met for the above-mentioned toxicological studies so that they can be used for a health assessment:

- The tests were carried out in compliance with GLP and in accordance with internationally recognized guidelines (e.g. in accordance with Regulation (EC) No. 440/2008, OECD guidelines, etc.).
- The tests were carried out for each product which is subject to approval as well as for the reference cigarette 3R4F (or 1R6F).
- The tests were each carried out in several technical and biological replicates in order to enable valid statistical evaluations (e.g. for *in vitro* cytotoxicity tests, at least 5 independent biological replicates are to be carried out for each individual product).
- Full study reports are available to verify compliance with relevant guidelines.

- The study reports contain the results as well as statistical analyses of these results that correspond to the state of the art in science and technology.
- The study reports contain statistical comparisons of the relevant values of each individual product with those of the reference cigarette.

6. Commentary on the Assessment Criteria

The adverse health effects of cigarettes result from the inhalation of emissions containing highly toxic substances. Some of these substances have mutagenic effects (causing mutations in the genetic material). The occurrence of mutations in the genetic material (genes) of cells is the prerequisite for the development of cancer. Mutagenic substances are considered carcinogenic. Due to mutagenic substances in tobacco smoke, smoking is carcinogenic.

Even without human or animal studies, it is possible to map properties of emissions, including an initial assessment of toxicity and potential mutagenic effects, by chemical-analytical methods as well as *in vitro* toxicity tests.

To compare health effects of heated tobacco products with those of conventional cigarettes, it is crucial to know:

A. … which substances are present in the emissions of heated tobacco products, or in what quantities they are found compared to emissions from conventional cigarettes. (see 6.1)

B. … which *in vitro* toxic effects are caused by the emissions of heated tobacco products and how these are to be assessed in comparison to the toxic effects of the emissions of conventional cigarettes. (see 6.2)

6.1 Emissions

WHO Recommendations on Emission Data

The WHO has published a priority list of toxic substances. These substances are generally found in tobacco smoke. Due to their toxicity, the WHO recommends this list of substances to be prioritised for testing and regulation. These substances are

prioritised since they are considered to contribute the most to health damaging effects besides a large number of other toxic substances that are also found in tobacco smoke. ((WHO 2019) page 170; Table 8.2. Emissions of combusted tobacco products considered and evaluated for inclusion in the lists of priorities for testing, reporting and regulation).

This list is considered to be an appropriate minimum scope of substances in emissions that should in any case be used for a health assessment of heated tobacco products. These values can then be compared with values of conventional cigarettes. In addition to the substances listed by the WHO, it would be desirable to have more comprehensive data on emissions from heated tobacco products.

Other Emission Data

Specific characteristics of heated tobacco products (e.g. product design, certain ingredients) could require, apart from the substances listed by the WHO, further information on emissions that are crucial to assess the health effects of the products. Which further information would be required for a health assessment depends on the respective product features and needs to be specified on a case-by-case basis.

Example Aluminium

Most of the currently known heated tobacco products have an aluminium coating around the tobacco rod. According to toxicological studies, aluminium compounds show neurotoxic and embryotoxic effects in animal experiments as well as negative effects on the male reproductive system and on the neuronal development of offspring through maternal exposure (EFSA 2008). Studies on aluminium dusts in the workplace (welding work) showed harmful effects on the lungs (pulmonary fibrosis) and the central nervous system (MAK-Commission 2007). According to the International Agency for Research on Cancer (IARC), occupational exposure during aluminium production is classified as carcinogenic to humans (Group 1) (IARC 2012).

It is therefore important for health reasons to verify whether this coating causes aluminium emissions that would be inhaled by the user when consuming the product. Any aluminium emissions from heated tobacco products with aluminium coating would need to be compared to aluminium emissions from cigarettes.

6.2 Toxicological Studies

There are a large number of *in vitro* test methods that can provide indications of toxicological effects in humans.

The following *in vitro* toxicological test methods are regarded by AGES to be the minimum that should be considered for a health assessment of heated tobacco products. These test methods are able to show the general toxicity of the emissions as well as their mutagenic effects.

Cytotoxicity Tests

These tests are simple tests that measure the general toxicity of a substance (or emissions). It is measured quantitatively whether the addition of the substance causes living cells (parts of body tissue) to die, or at which doses of the substance how many cells die (simplified). It is tested whether, or to what extent a substance is toxic. The exact mechanism of action of the substance that leads to the death of the cells cannot be deduced from the test results. There are many different types of cytotoxicity tests. The neutral red uptake assay (NRU assay), for example, is a common cytotoxicity test (Repetto et al. 2008).

Mutagenicity Tests

There are toxicological tests that can specifically show whether substances induce mutations. A well-established test is the bacterial reverse mutation test (AMES test). It tests whether a substance induces so called point-mutations in bacteria. An internationally recognised guideline is available for the bacterial reverse mutation test (OECD Guideline 471). To enable the inclusion of relevant studies of heated tobacco products in a health assessment, they should comply with OECD Guideline 471 which ensures the quality of the studies.

However, since bacteria are biologically very different from human cells, it is common to carry out additional mutation tests in mammalian cells. Furthermore, with the common mutation tests in mammalian cells it is possible to detect other types of

mutations than point mutations. Internationally recognised guidelines are available for various mutation tests in mammalian cells (OECD Guidelines 476, 490 or 487). At least one of these tests should in any case be used for a health assessment of heated tobacco products. As a prerequisite, these tests must be performed according to the guidelines (OECD Guidelines 476, 490 or 487) to ensure the quality of the studies.

7. Assessment of Submitted Documents

The assessment body records in its expert opinion whether the product that is subject to authorisation complies with the requirements of the TNRSG when used as intended.

This involves, among other things, a review of the submitted documents

- for completeness, plausibility and conclusiveness,
- whether the product that is subject of the application falls under the definition of a smokeless tobacco product or a tobacco product for smoking,
- with regard to the labelling and appearance of the product, the packaging and the outer packaging,
- on the presence of prohibited additives,
- whether the product that is subject of the application could have more harmful effects than a cigarette.

When assessing the data/information referred to in point 5 of this guideline, the assessment body can only conclude that no indication of possible more harmful effects was found if:

- any emission measurement values of the heated tobacco product according to point 5.1 A are statistically significantly ($p<0.001$) lower than those of the reference cigarette.
- any *in vitro* toxicological studies according to 5.1 B show lower toxicity for the heated tobacco product than for the reference cigarette.

However, even if these criteria are met, this does not exclude the possibility that data other than those referred to in this guideline may indicate that the product subject to authorisation may have more harmful effects than the product used for comparison.

8. References

CDC Centers for Disease Control and Prevention https://www.cdc.gov/tobacco/basic_information/health_effects/index.htm

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9. Further Reading

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