Agence nationale de sécurité du médicament et des produits de santé

RÉPUBLIQUE FRANÇAISE

7 July 2022

Temporary Scientific Committee Opinion of 08 June 2022

"Philips Respironics ventilation devices affected by June 2021 recall: Review of data available and recommendations"

In the context of the worldwide recall of certain Philips ventilators and CPAP generators, ANSM convened an ad hoc Temporary Scientific Committee (TSC) on 8 June 2022 in order to better understand the potential risks associated with the use of these defective devices.

This TSC is composed of representatives of associations of users of the health system as well as qualified persons for their expertise in general medicine, pneumology, toxicology, medical devices and epidemiology.

The first part of this meeting was dedicated to public hearings broadcast live on ANSM's Youtube channel. Representatives of patient associations, home health care providers, learned societies, epidemiological studies (France, Canada, Sweden), the Food and Drug Administration (FDA), as well as the Philips Respironics company were heard.

The replay is available in French and English.

The second part of the meeting was closed. The deliberations of the expert members led to the drafting of this opinion.

For all the information concerning this TSC (agenda, decision to set up, etc.), see: https://ansm.sante.fr/evenements/comite-scientifique-temporaire-appareils-de-ventilation-philipsrespironics-concerned-by-the-june-2021-recall-and-status-of-available-data-and-recommendations

Expert members:

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Olivier LAPREVOTE – Toxicologist – Paris Cité University
Robert GARNIER – Medical Toxicologist – Poison Control and Toxicovigilance Centre - Paris
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Anne-Sophie DUFLOS – Representative of the association "Vaincre la mucoviscidose"
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1- General context and June 2021 Field Safety Notice

On 10 June 2021, ANSM was informed by Philips Respironics of its intention to recall and replace certain ventilators and CPAP (Continuous Positive Airway Pressure) generators worldwide, following the identification of a possible problem with the sound abatement foam present in these medical devices.

CPAP generators are used by patients at night as part of their treatment for obstructive sleep apnoea-hypopnoea syndrome. Ventilators provide assisted ventilation for patients with chronic respiratory failure. These devices are subject to medical prescription and provided to patients by home healthcare providers.

Two risks were identified by Philips Respironics:

- a risk of exposure to 2 volatile organic compounds (VOCs):
  - Dimethyldiazene (CAS Number: 503-28-6);
  - 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)-phenol, (CAS Number 17540-75-9).
- a risk of exposure to particles stemming from foam degradation.

The potential risks identified by Philips Respironics and communicated via the Field Safety Notice are:

- "The potential risks of particulate exposure include: irritation (skin, eye, and respiratory tract), inflammatory response, headache, asthma, adverse effects to other organs (e.g. kidneys and liver) and toxic carcinogenic effects. To date, Philips Respironics has received several complaints regarding the presence of black debris/particles within the airpath circuit (extending from the device outlet, humidifier, tubing, and mask). Philips also has received reports of headache, upper airway irritation, cough, chest pressure and sinus infection.";
- "The potential risks of chemical exposure due to emission of chemicals include: headache/dizziness, irritation (eyes, nose, respiratory tract, skin), hypersensitivity, nausea/vomiting, toxic and carcinogenic effects. To date, Philips has received no reports of patient impact arising (or alleged to arise) from this risk."

In France, the Philips recall programme concerns approximately 350,000 CPAP devices and 29,500 ventilators.

As soon as the recall was announced, ANSM, in consultation with the different stakeholders (learned societies, home healthcare providers and patient associations), issued guidelines advising users not to discontinue their treatment pending the replacement of their device. Since then, regular meetings are held with the parties involved, and ANSM is in regular contact with the manufacturer to track progress in device replacement rates.

2- Aims of the Temporary Scientific Committee (TSC) and questions put to the expert members of the TSC

The aims of the TSC were as follows:

- conduct a review of the available data on the potential risks of using the Philips Respironics devices affected by the recall of 10 June 2021;
- give an opinion on this data and recommend further studies if necessary;
- update, where applicable, the guidelines issued by ANSM on continued use of the devices pending their replacement.

Five questions were put to the experts:

- Is it possible to assess the potential and, where applicable, known risks associated with the use of the Philips Respironics devices affected by the recall of June 2021, in respect of VOCs and particles potentially emitted?
- If the answer to question 1 is yes, what are the short-term / long-term risks that may be attributable to the devices affected by the recall, in respect of VOCs and particles potentially emitted?
- If insufficient data are available, which further studies / analyses need to be conducted?
- Is there a need to update the ANSM guidelines in relation to treatment continuity, in particular, for the 3 types of devices affected by this recall: CPAP generator and life-support or non-life support ventilator?
- For each of these aforementioned devices, it is possible to issue machine replacement prioritisation criteria?

3- TSC review

The TSC expert panel includes representatives of health system consumer associations, as well as experts in general medicine, respiratory medicine, toxicology, materials and their behaviour under operating and storage conditions, medical devices, and epidemiology.

Prior to the meeting, all members received the toxicology test reports sponsored by Philips Respironics and forwarded by Philips Respironics to ANSM on the date of the meeting. They were also provided with a summary of these reports prepared by ANSM, an analysis of the medical device vigilance data relating to the devices affected by this recall, the publications pertaining to the relevant epidemiological studies, and, finally, extracts of the information available on the ANSM, FDA, and Philips Respironics websites.

The first part of the TSC meeting was given over to public interviews with the stakeholders affected by this recall: patient associations, home healthcare providers, epidemiological study leads, medical device vigilance data analysis reviewers, learned societies, and foreign competent authority.

3.1 Design of the devices discussed at the TSC meeting

The experts raised the following points during the discussions:

- The design of the devices involves risks of particle emission in the respiratory circuit. This choice of design (foam in direct contact with the airpath circuit) by Philips Respironics should be accompanied by thorough knowledge of the materials, their behaviour under mechanical, thermal and time constraints, and their biocompatibility. There is an information gap in this respect in the documents supplied by Philips Respironics.

3.2 Preclinical studies conducted by Philips Respironics on the devices discussed at the TSC meeting

The test reports reviewed concerned the testing of VOC emissions from DreamStation devices, and the assessment of polyester-based polyurethane (PE-PUR) sound abatement foam degradation.

The experts raised the following points during the discussions:

- The overall testing strategy implemented by Philips Respironics is unclear. For this reason, despite the extensive investigations already conducted, it is not possible to obtain an accurate assessment of the health risks for users of the devices affected by the recall. The overall methodology and relevance of the studies appears to be poorly presented and poorly designed; the choice of tests conducted needs to be justified.

- The initial exposure assessment conducted by Philips Respironics is not robust and does not permit an interpretation of the risk from using these devices. In particular, the data presented leave some doubt regarding the actual presence of the substances announced by Philips in June 2021 or even regarding the emission of these substances from the devices affected.

  The experts are of the view that there was probably some confusion in the initial findings between the spectrum of dimethyldiazene (DD) and that of acetone.
  As a result, the presence of DD, the substance announced as a carcinogen by Philips Respironics in June 2021, has not been established.
  This point was confirmed by Philips Respironics after the meeting.

- The further tests conducted by Philips Respironics since June 2021 have some methodological flaws. It would be necessary to construct a test plan based on, for example:
  - The content of the material safety data sheets;
  - The composition of the materials and the type of PUR used;
  - The design of the airpath circuits;
  - The use-by date defined;
  - The setting in which the devices are used;
  - Their packaging.

  The tests must be carried out, for example, according to the behaviour of the PUR foam over time. No evidence has been furnished proving that artificially aged foam is equivalent to naturally aged foam. Given this uncertainty that both degradation processes are identical, it is necessary to compare foam degradation between old foam and artificially aged foam.

At this stage, it is not possible to determine whether the VOC emission issue stems from foam degradation or from ventilator emissions.
Materials, such as PUs, change over time. Conducting an analysis at T_0 and at $T_{aged\ device}$ is not representative of the potential VOCs received by the patient. A pertinent ageing study with regard to device use is needed to accurately determine the compounds emitted during use and the trends in these emissions, as well as their potential toxicity. In artificial ageing studies, the behaviour of the foam over time should be assessed by applying pertinent parameters in terms of routine device use, such as mechanical constraints, humidity, etc. These tests are expected to be conducted not only on new devices, but also on previously used devices.

The tests for which results have been provided by Philips Respironics are described as having been conducted on devices with and without humidifier, but only one type of result is given (without humidifier). Philips Respironics has specified that the results for both types of devices are identical; however, no proof of this has been provided.
Given that some tests were conducted on devices and their packaging, the VOCs detected in the first days of the emission tests might also have originated from the packaging. It could be recommended, as a general rule, that the service provider run all new machines for 48 hours before setting them up for the patients in order to remove the maximum amount of substances present in a new device.

Moreover, as VOCs of the same kind as those detected by the tests performed are usually found in indoor air in homes, the interpretation of the results should account for the usual concentrations of these substances in the air of homes.

Finally, the risk assessment as conducted, based on the characterised emissions, is unacceptable for several of the substances identified, given the reference toxicological values adopted or constructed, the uncertainty factors adopted, the substances selected for read-across readings, etc.

- Particle emissions are inadequately characterised.

  The particle emission risk assessment must be improved. The particles need to be better characterised in quantitative and qualitative terms. Information on the granulometry, size, distribution and their chemical identification is needed. In fact, providing results expressed solely in terms of PM_{10} and $PM_{2.5}$ is not sufficient, as even at low doses, these particles can have an effect on health.

Therefore, the risk assessment conducted by Philips Respironics is not robust, and the experts are not in a position to assess the risk based on the tests furnished by Philips Respironics.

3.3 Epidemiological studies

The following epidemiological studies were presented at the interviews:

- *Research letter - An Association between Positive Airway Pressure Device Manufacturer and Incident Cancer? A Secondary Data Analysis.* Kendzerska T et al. American Journal of Respiratory and Critical Care Medicine 2021; 204(12):148461488 (Canadian study);
- *Research Letter - Health risks related to polyurethan foam degradation in CPAP devices used for sleep apnoea treatment.* Palm et al. The European Respiratory Journal 2022; 59(5):2200237 (Swedish study);
- *Research Letter - Cancer risk in adherent users of polyurethane foam-containing CPAP devices for sleep apnoea.* Justeau et al. The European Respiratory Journal 2022 May 20;2200551, early view (French study).

The experts' general observations are as follows:

- Two of these three epidemiological studies, conducted using pre-existing databases, find no link between Philips Respironics CPAP device use and overall cancer risk or lung cancer risk (French study and Canadian study). The Swedish study, after merely two years of follow-up on average, finds an overall excess risk of cancer and an excess risk of lung cancer among CPAP device users in districts where Philips Respironics devices represent over 80% of the devices supplied to patients. This is probably explained by the fact that, in these districts, a higher incidence of cancer (lung cancer in particular) is also recorded in the general population.

- At this stage, in the light of the data available, there is no scientifically established excess risk of cancer at 5 years (current follow-up of the studies).
- Nevertheless, these three epidemiological studies cannot in themselves rule out any cancer risk associated with the use of Philips Respironics CPAP / ventilation devices, especially as the sleep apnoea patients included in these studies were not followed up for enough time on average for a potential excess risk of cancer associated with the use of these devices to appear.
- Data with 7 to 10 years or more of follow-up are needed, detailing risks according to different cancer sites, and the cumulative exposure time to CPAP / ventilation devices.
- Each of the three studies cited above involved methodological limitations, introducing uncertainty into the interpretation of their findings.
- It was noted that the learned respiratory medicine societies interviewed consider the cancer risk associated with the use of these devices to be low, whereas the risks associated with discontinuing treatment are established.
- The Swedish study demonstrates a link between the use of Philips Respironics devices and moderate worsening of bronchial obstruction, which is not observed with devices from other suppliers; however, this study was unable to account for tobacco use in its analyses, which might explain the difference observed between the use of CPAP Philips Respironics devices and other CPAP devices.
- It was noted that the learned societies and home healthcare providers interviewed are willing to continue the epidemiological studies and use current databases. The learned societies interviewed pointed out the lack of benefit of setting up ad hoc cohort studies, given the period of follow-up needed (more than ten years) to demonstrate a potential excess risk of cancer. Moreover, ANSM is continuing the project to use cross-referencing data obtained from the National Health Data System and other provider databases.
- As regards prioritising the replacement of devices, “The FDA has recommended, and Philips has accepted, the implementation of a prioritization approach that ensures patients who are most vulnerable to poor healthcare outcomes with continued use or ceasing use of the recalled products receive replacement devices as quickly as possible”.

4- Conclusion

TSC response to question 1 on the assessment of potential risks:

It is not possible to assess exposure to potentially emitted VOCs and the associated risks based on the data currently available (preclinical data and epidemiological data). Beforehand, it is essential that the assessment strategy be clarified and elucidated, in order to enable the use of the findings of the trials previously conducted. The TSC committee has proposed some avenues (see above).
In the case of particles, they must be characterised quantitatively, physically and chemically using devices aged under normal conditions of use, with artificial ageing tests merely serving to confirm and elucidate the observations made on devices actually used by patients. The epidemiological data currently available do not provide reliable findings as to the potential health impact of particles generated by foam degradation in the devices affected by the recall.

TSC response to question 2 on the short/long-term risks attributable to the devices:

The carcinogen allegedly identified in June 2021 was dimethyldiazene (DD). The experts are of the view that DD was probably confused with acetone. Therefore, the risk associated with this VOC emitted at early stages cited by Philips in June 2021 is not established due to a lack of evidence of its presence.
In addition, the impact of VOCs potentially emitted at later stages and particle emissions also need to be assessed. The data needed to address these issues are not currently available.

TSC response to question 3 on studies and supplementary analyses to be conducted:

A full review of the programme of exposure tests conducted by Philips Respironics is needed.
The epidemiological studies initiated should be continued to particularly assess risks of cancer and obstructive diseases, expressing the findings according to the cumulative exposure time and, for cancers, targeting patients exposed beyond 7 to 10 years and studying different cancer sites separately.
Assessment of the feasibility of an epidemiological study using home healthcare provider data linked with data from the National Health Data System also needs to be continued.

TSC response to question 4 on recommendations to continue treatment:

Device replacement must be continued according to the schedule set out by the ANSM decision, as the non-conformity of the devices in question has been established (foam degradation). The conformity of the replacement devices needs to be confirmed.
The guidelines issued by ANSM in June 2021 remain valid, especially given that the risk associated with dimethyldiazene is probably no longer established.
As a reminder, the current guidelines are as follows: “patients must continue to use their devices. Discontinuing use involves an established short-term risk, for example drowsiness which can be a factor in accidents, excess cardiovascular risk, or worsening of respiratory failure. According to the initial data available, the cancer risk associated with the use of the ventilators and CPAP devices in question has not been established.”

They may be reviewed once further assessments, particularly in relation to delayed VOC emissions, are available, as well as the assessment of particulate emission.

TSC response to question 5 on the possibility of setting replacement prioritisation criteria:

No recommendation.

The communication issued by Philips on 28 June 2022 on its website regarding its test programme does not call into question the conclusions of the TSC.
On the basis of this expert opinion, ANSM will require Philips to clarify its risk assessment strategy, and in particular the tests aimed at allowing a relevant analysis of the situation.