Superior Health Council

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Peptide Receptor Radionuclide Therapy

In this scientific policy advisory report, the Superior Health Council provides a risk assessment (efficacy, toxicity, safety and radioprotection) for Peptide Receptor Radionuclide Therapy (PRRT) with Lutetium-177 and Yttrium-90 for patients diagnosed with gastroenteropancreatic neuroendocrine tumours.
This advice also provides recommendations for further research and specific information on the utility and restrictive conditions.

01 august 2012

1. INTRODUCTION AND ISSUES

The Federal Agency for Nuclear Control (FANC) received a question about the clinical use of lutetium-177 (Lu-177) labelled peptides as part of an oncological treatment for malignant tumours of neuroendocrine origin. The FANC invokes the Superior Health Council (SHC) for advice on this matter since article 51.1.1 of the Royal Decree of 20/7/2001 (RD/ARBIS/RGPRI) states that "for every medical act involving ionizing radiation, the potential benefit for the patient and the society should be considered with regards to the potential detriment to the patient, his environment and the society. This consideration on the use of ionizing radiation should be made in particular if it concerns a medical act introduced in a clinical setting as a general application or when first licensed".
The SHC appointed an expert panel to address these specific questions, but will also cover Yttrium-90 (Y-90) labelled peptides as part of an oncological treatment for malignant tumours of neuroendocrine origin in its recommendations.

Question 1: Is there sufficient evidence of clinical benefit of Lu-177 labelled peptides as part of an oncological treatment to justify the ionizing radiation risks to the patient, his family, personnel and environment?

Question 2: In case of a positive advice for question 1, could you formulate the conditions (e.g. restricted use) for application of Lu-177 labelled peptides and the required (additional) training for personnel involved in this treatment?

2. ADVICE

Question 1: The expert panel unanimously agrees that today sufficient clinical evidence is available for the use of Lu-177/Y-90-labelled peptides for treatment of neuroendocrine tumours (NET). The use of such treatment, owing to the rare nature of such tumours should however be integrated in a complex armamentarium of treatments and cannot be considered as 'routine'.

The SHC considers that the following guidance should be established for the indication of such treatment:

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- Histology-proven NET of the gastroenteropancreatic (GEP) tract (with inclusion of lung carcinoid tumours), especially –but not exclusively- with WHO grade 1-2, not amenable to curative (i.e. surgical) treatment;
- Histology-proven tumours of neuroendocrine nature of other origin (e.g. paraganglioma, metastatic pheochromocytoma or medullary thyroid carcinoma), not amenable to curative treatment, such as by surgery or external beam radiation therapy, nor to other approved therapies;
- Tumour(s) must display a high density of somatostatin receptors (subtype 2-SSTR2), by means of functional imaging using In-111 or Ga-68 labelled somatostatin analogs[1];
- Prescription under the consensus declaration of a multidisciplinary oncology consultation (MOC), after careful consideration of other palliative options, especially biotherapies using registered molecules in pancreatic tumours;
- Adequate general condition (i.e. Karnofsky performance status > 50), renal, liver and haematological functions are required.

Question 2: The SHC proposes the following (restrictive) conditions for clinical use of Lu-177/Y-90-labelled peptides:

- This treatment should be carried out in accordance with the applicable pharmaceutical legislation. Accordingly, the clinical use of such radiopharmaceuticals remains under the legislation on the use of drugs in general, which is the competence of the Federal Agency for Medicines and Health Products (FAMHP); appropriate arrangements should be made with this administrative body. The notion of orphan drug for a target of a few hundreds of patients in total in Belgium per year should be taken into account, whereof only 20-25 % might be eligible according to Question 1. Hospital exemption as foreseen by the European Directive (CE) n° 1394/2007 for Advanced Therapy Medicinal Products (ATMP's) could be considered. The SHC notes that the FAMHP was invited to share the discussion but was not in the position to participate, meaning that the pharmaceutical aspects were not discussed further, remaining under the strict competence of the FAMHP for what relates to the drug itself, the FANC being competent for the use of radiopharmaceuticals as such with regards to radiation protection;
- According to this, a licensed radiopharmacist is in charge of directly supervising the radiolabelling procedure and subsequent manipulations of the radiopharmaceutical. Staff members should receive the highest protection level possible, in particular by use of monitoring extremity doses during preparation and administration and also by wearing direct reading dosimeters during these activities;
- The treatment must be carried out by a specialist in Nuclear Medicine, licensed to use radiopharmaceuticals for therapeutic purposes in hospitalization, in an institution duly licensed for the retention and use of Lu-177 and Y-90 (art. 53.1 and 53.4 of the RD). ;
- The treatment requires a hospital stay in a dedicated radionuclide therapy room, licensed for Lu-177/Y-90; patients can be discharged when a dose rate below 20µSv/h at 1 m distance is reached. Patients must receive at discharge a written document with instructions related to radiation protection issues for their family and neighborhood. In particular, the document should focus on the protection of children and potentially pregnant women, as well as for contraception for the 6 months following the last foreseen treatment. For generic guidelines on this topic, it is referred to a previous advice of the SHC (No 7221);
- A licensed radiation physicist is required for supervising all radiation protection issues related to the patient including performing individual dosimetry for prevention of normal organ toxicity (see art. 51.7.1 of the RD 20/07/2001 and appendix 1);

[1] For In-111, the reference is the Krenning scale (Kwekkeboom et al., 2008) ; this could be translated to whole-body scanning with Ga-68-labelled peptides. Regarding the Ga-68-PET, it can be used to identify potential patients but not to actually score the uptake.

- All procedures regarding staff and public radiation protection issues should be validated beforehand by a licensed expert in Health Physics, who should be either present on site or available at all times;
- Hospitals licensed for clinical use of Lu-177/Y-90 labelled peptides are strongly encouraged to put continued efforts in training all personnel involved in this field. Medical staff, radiopharmacists and physicists responsible for this treatment are encouraged to update their skills on a regular basis in order to further improve the safety standards in their hospital. Centers implementing this treatment are encouraged to accept guidance from an expert center (that are available in neighboring countries), including a working visit by physicians, pharmacists and physicists.

3. METHODOLOGY

Given the questions from the FANC were raised following a combined request by the University of Louvain (Prof Dr. E. Van Cutsem and C. Deroose) and Institut Bordet (Prof. Dr. A. Hendlisz and P. Flamen), it was decided to invite representatives of these groups for further information and elaboration. Prof. C. Deroose and A. Hendlisz attended the meeting and gave a comprehensive review of the current status in the field. They subsequently replied to questions of the experts but did not participate to further discussions.

All experts and invited parties agreed on the confidentiality rule. No expert had to disclose interests (especially financial) with the treated matter. As a matter of fact, all physicians are or have been working to some extent in the field of NET over the last years and are clearly keen to see progress in Belgium in a field that has been widely explored in Europe (Ambrosini et al., 2011). Therefore, validation of the advice was requested from independent experts from neighboring countries. The advice is based on the scientific evidence from the literature for what concerns medical aspects, and on scientific literature and experts' opinions for the radiation protection issues.

Within the context, the advice can be considered as a formal reply to a regulatory issue; accordingly, references are indicative but not intended to give an exhaustive review (meta-analysis type) of the topic.

4. FURTHER DETAILS AND ARGUMENTATION

Keywords

Keywords	**Mesh terms***	**Sleutelwoorden**	**Mots clés**	**Stichworte**
Radioisotopes	Radioisotopes	Radioisotopen		
Lutetium	Lutetium	Lutetium		
Yttrium	Yttrium	Yttrium		
Neuroendocrine Tumours	Neuroendocrine Tumours	Neuro-endocriene tumoren		
Peptide Receptors	Peptide Receptors	Peptide Receptoren		
Therapy	Therapy	Therapie		

List of abbreviations

ATMP	Advanced Therapy Medicinal Products
ESRF	End-Stage Renal Failure
FAMHP	Belgian Federal Agency for Medicines and Health Products

FANC	Federal Agency for Nuclear Control
GEP	Gastroenteropancreatic
Lu-177	Lutetium-177
MOC	Multidisciplinary Oncology Consultation
NET	Neuroendocrine Tumours
PRRT	Peptide Receptor Radionuclide Therapy
QOL	Quality Of Life
RD	Royal Decree
SHC	Superior Health Council
SOP	Standard Operating Procedure
SSTR2	Somatostatin Receptors Subtype 2
WHO	World Health Organization
Y-90	Yttrium-90

4.1 Introduction

Together with the FANC request, the expert panel received a copy of the letter of the applicants, Prof. Dr Christophe Deroose and Eric Van Cutsem from UZ Leuven and Prof. Dr Patrick Flamen and Alain Hendlisz from Institut Bordet- to the Minister of Health. This letter asks for reimbursement of Peptide Receptor Radionuclide Therapy (PRRT) in Belgium. Currently, Belgian patients not eligible for clinical trials with PRRT are sent abroad for this specific kind of treatment and often costs are reimbursed. However, for an identical treatment in a Belgian hospital no reimbursement is available. The letter to the Minister of Health refers to PRRT as peptides labelled with Y-90 or Lu-177. However the advice request from the FANC addressed to the SHC only refers to Lu-177. Because we do not have convincing definitive evidence today that one radionuclide outperforms another in this kind of PRRT (e.g. from data of (a) large multicentric randomized trial(s)), recommendations for Lu-177 as well as Y-90 labelled peptides were discussed and are proposed.

4.2 Question 1:

Is there sufficient evidence of clinical benefit of Lu-177 labelled peptides as part of an oncological treatment to justify the ionizing radiation risks to the patient, his family, personnel and environment?

PRRT is a type of treatment of malignant tumours that was initially developed in the early 90's (Kwekkeboom et al., 2010; Ambrosini et al., 2011). It is based on the specific property of some tumours to bear a high density of hormonal receptors (Maecke et al., 2011). Until now, mainly somatostatin receptors subtype 2 (SSTR2) have been targeted with success in the clinics, using somatostatin (peptide) analogs labelled with In-111, Y-90 and Lu-177. In-111 has now been abandoned because of insufficient efficacy and because of the toxicity risk to the bone marrow. Two main peptides are now being used, [DOTA^0-Tyr^3-Thre^8]-octreotide (DOTATATE) and [DOTA^0--Tyr^3]-octreotide (DOTATOC), labelled with either Y-90 or Lu-177 (see appendix 2). Looking at literature data, covering clinical studies on PRRT for metastatic neuroendocrine tumours (NET) of GEP origin over the last decade, there is reasonable evidence that this kind of treatment deserves to be part of the therapeutic armamentarium in such patients. More than 1000 patients treated in Basel with Y-90-DOTATOC, as well as large datasets from Milan confirm the positive findings. In Rotterdam (after initial pioneering experience with In-111-pentetreotide and transient use of Y-90-DOTATOC), hundreds of patients with GEP NET were treated by means of Lu-177-DOTATATE (Kwekkeboom et al., 2008). All studies consistently showed the overall safety of the application (Claringbold et al., 2010; Bodei et al., 2011).
The benefit rate in cumulated studies is in the range of 10-74 % with peptides labelled with In-111, Y-90 or Lu-177. The meaning of benefit however varies between publications, including objective responses and stable disease but also symptomatic responses and improvement of quality of life (QoL). Objective responses as assessed by normative ways such as RECIST criteria (complete or

partial responses, i.e. more than 50 % tumour shrinkage) were observed in 0-34 % of the patients. No single randomized study on the use of PRRT was published so far. Comparisons with historical controls are in favor of PRRT. It must be kept in mind that such studies are also lacking for most of the alternative treatments, such as chemotherapy. Only limited randomized double-blinded studies are available for justifying the use of long-acting somatostatin analogs in this setting although it is the standard treatment for more than fifteen years. This is related to the low prevalence of NET and their heterogeneity (GEP, pulmonary origin, secreting, non-secreting, WHO class of differentiation1-2/3, ….).

Toxicity was overall low with minor acute side effects and a limited probability of delayed side effects that include impairment of renal function sometimes leading to end-stage renal failure (ESRF), liver failure in patients with extensive liver disease and myelodysplasia or acute myeloblastic leukemia as a consequence of bone marrow irradiation, especially in patients previously treated with chemotherapy. The number of patients reported with such toxicities does not exceed 5 % of the total populations. It must be kept in mind that renal toxicity has been very significantly reduced by the use of amino acid infusions that compete with the renal cortex reuptake of the labelled peptides by proximal tubular cells (Vegt et al., 2010), as well as by the more recent development of Lu-177. Besides these significant side effects, less severe toxicity is reported including nausea and vomiting (due to the amino acid infusion regimen), transient and incomplete hair loss (with Lu-177) and tumour pain due to acute irradiation of tumours with high uptake (Kwekkeboom et al., 2008).

Although randomized studies are nowadays lacking for PRRT, the panel concludes that the presented data (multiple large datasets from different hospitals) confirm the possible clinical benefit for patients suffering GEP NETs and pulmonary carcinoids refractory to cold somatostatin analogues, if imaging confirms the sufficient binding of somatostatin receptors, being the minimum criterion for patient selection.

The indication for PRRT should be limited to tumours with very high SSTR2 expression as demonstrated by a high uptake of the diagnostic agent In-111-pentetreotide (commonly referred to as the Krenning scale) (Kwekkeboom et al., 2008), especially the well-differentiated GEP-NET, including the lung carcinoid tumours (Kwekkeboom et al., 2011) and can be considered in other tumours of neuroendocrine lineage (e.g. paraganglioma, pheochromocytoma, medullary and poorly or dedifferentiated thyroid carcinoma,…) only as a last option, when all therapeutic options have been explored and failed, since in these indications, only anecdotal reports are available. It must be kept in mind that the most aggressive tumours (i.e. WHO grade 3) are usually better treated with chemotherapy. Further, biotherapies are now available (sunitinib and everolimus) for advanced pancreatic tumours, in which chemotherapy is a valid option (streptozotocin) but is not available in Belgium.

The SHC suggests that all candidates for PRRT are discussed in a multidisciplinary staff meeting for oncology patients, by a panel of specialists comprising for instance one medical oncologist (in the broad meaning of it), one surgeon, a pathologist and a nuclear medicine physician. This panel will finally identify the indication after careful review of the alternatives. This must be encouraged since progress in this field was recently made by several biologicals (e.g. randomized data available for pancreatic NETs, see for instance, Pavel et al., 2011) and indications for PRRT should always be considered in the light of the most recent clinical data.

4.3 Question 2:

In case of a positive advice for question 1, could you formulate the conditions (e.g. restricted use) for application of Lu-177 labelled peptides and the required (additional) training for personnel involved in this treatment?

Preliminary remark

Some issues directly refer to current legislation and do not deserve further discussion. They are therefore listed in the advice itself, with, when appropriate, legislation references.

4.3.1. Patient protection

Safety data that were discussed show that the normal organs at risk for delayed and sometimes severe toxicity are the kidneys and bone marrow. If not appropriately dealt with, such toxicities might result in treatments with insufficient dosage and efficacy. Conversely, the systematic use of fixed activities ('doses') may lead to unexpected toxicity. Nephrotoxicity is nowadays prevented by using amino acid infusion (Vegt et al., 2010) as well as by performing some basic dosimetry, especially in risk patients. This is foreseen by the European Directive 97/43. In depth expertise in this particular topic is available in Belgium (Pauwels et al., 2005; Walrand et al., 2011). A further reduction of the risk is obtained by the switch towards Lu-177 instead of Y-90. However, this kind of radionuclide therapy warrants guidance from a radiation physicist, trained in patient dosimetry. Standard operating procedures (SOP's) should be in place to deal with normal organ dosimetry where needed, in order to prevent toxicity and SOP's should be updated on a regular basis, according to the most recent insights.

Lu-177-labelled peptides offer the advantage that, due to the emission of low-energy gamma rays, imaging obtained after the infusion of a first treatment (e.g. 7.4 GBq Lu-177-labelled peptide) allows to determine the maximal allowed activity to limit the renal absorbed dose to 23 Gy[2], a dose that would result in less than 5 % renal toxicity by 5 years post-treatment (Barone et al., 2005; Bodei et al., 2008; Bodei et al., 2011). This is more complicated, although feasible with Y-90-labelled peptides (Walrand et al., 2011). In both cases, the total administered activity can be calculated individually and reduced from the planned treatment if appropriate.

4.3.2. Personnel protection (articles 20.1, 25, 27, 29, 30 of the RD 20/07/2001)

Safety of personnel, involved in preparing the radiopharmaceutical, in administration and in hospitalization, should be optimized and guaranteed. The radiolabelling procedure is safe in experienced hands (Lu-177 DOTATATE 0.5-1.5 mSv eff dose per 100 labelling procedures, finger doses <10 % of legal limits). Circulated literature data and presented data from UZ Leuven show that both Lu-177 and Y-90 DOTATOC/TATE can be safely prepared on a regular basis. However, it is known that high absorbed radiation to the fingers can be problematic especially for Y-90 in untrained hands. Therefore, it is advised for the staff in charge of preparation and injection to wear extremity dosimeters and direct reading dosimeters for the first year of practice in order to establish the extent of the actual risk and establish good practice. The hot lab personnel must work under strict guidance of a radiopharmacist, licensed and trained according to up-to-date standards (art. 46 of the RD 20/07/2001). Training should consist of an initial observation phase, followed by gradual involvement in actual handling of the radiopharmaceutical. In case of high patient throughput significantly affecting the effective doses to the staff and especially absorbed doses to the extremities, automatic syntheses techniques should be considered. Education and training tools can be found for instance as deliverables[3] of the ORAMED FP7 project (Rimpler et al., 2011).

[2] The 23 Gy threshold has been defined from external beam radiotherapy (EBRT) and was shown not to be valid for internal radiation therapy, for which Biological Effective Dose (BED) can by far exceed the plain absorbed dose (Barone et al., 2005; Bodei et al., 2008). It is beyond the scope of this report to develop and discuss this concept. The most recently approved and appropriate dosimetry model should be taken into account, e.g. Recommendations from the EANM Dosimetry Committee (Lassmann et al. 2011).

[3] (http://www.oramed-fp7.eu/en/~/link.aspx?_id=230CFF41CFF04FB4AF46B6DD7E4D6295&_z=z)

4.3.3. Protection of the public (articles 34, 51.2.4, 54.8.2 of the RD 20/07/2001, Radiation Protection 122 of the E.C., Safety Reports Series n° 63 of the IAEA)

Taking into account the urinary excretion of the radiopharmaceutical (> 65 % at 24h) and the dose rate at one meter distance, the SHC recommends a hospital stay of at least 24h in a licensed and dedicated radionuclide therapy room. Urinary contamination can be an issue and nurses should be trained to be aware of this. SOP's should be available and contain the following information: basic requirements for hospitalization, collecting excreta (e.g. urine), management of radioactive waste, criteria for patient's discharge, contamination checks and decontamination procedure, emergency care and resuscitation,... The health physics expert should check the room for contamination (beta or gamma) following patient discharge. Patients should receive oral and written guidelines on radioprotection in view of reducing the radiation burden to their family, friends as well as to the general public. This information should explicitly cover the issue of contraception since for both female and male patients procreation must be strictly avoided for at least 6 months after the last administration of the treatment.

4.3.4. Protection of the environment

All wastes should be dealt with according to the relevant legislation and established rules (articles 34, 35 and 37 of the RD). Besides the national legislation, it can also be referred to some extent to previous advice of the SHC (no 7221). For therapies with Lu-177 (t1/2 6.7 days), particular attention is needed due to the presence of Lu-177m (T1/2 160.9 days) (Bakker et al., 2006). According to manufacturers' specifications, Lu-177 contains less than 0.4kBq Lu-177m/MBq Lu-177 (at the end of neutron irradiation), when produced by the [Lu-176, n, Lu-177] reaction via thermal neutron bombardment of enriched lutetium oxide.

Material used for radiolabelling and administration of the peptides (used vials, QC specimens, syringes,…) has to be kept apart and evacuated according the legislation (e.g. storage until decay). Urine should be collected during the first 24h (hospitalization, see 4.3.3). 65-70 % of the activity will be thus collected, meaning 5.2GBq Lu-177 (discharge limit 1.9kBq/l) and 2MBq Lu-177m (discharge limit 0.59 kBq/l). Decay storage of ca. 100 days will bring the activity of the Lu-177 in compliance with the discharge limit; Lu-177m is already within the limits. This is only valid for liquid waste and frozen material cannot be dealt with as solid waste. Collection in tank reservoirs should be avoided because of possible deposition of the long lived Lu-177m. Radiolabelling with carrier-free Lu-177 should be preferred in the Belgian context. It must be kept in mind that such production is supposed to be more expensive and will impact the budget.

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6. APPENDICES

Appendix 1. The use of radiopeptides, i.e. peptides labelled with therapeutic radionuclides, such as Lu-177, Y-90, or any other intended therapeutic radionuclide, requires the involvement of an authorized nuclear medicine medical physics expert.

In the institution where the patient is treated, this radiation physicist should be closely involved and needs to be familiarized with the use and quality assurance of all devices that could be used for the individual determination of the radiation dose. In particular, dedicated protocols must be established to determine with acceptable accuracy the dose to the organs at risk, i.e. the kidneys and bone marrow. These may include all imaging modalities (e.g., gamma camera, SPECT, PET, SPECT / CT, PET / CT) and all non-imaging devices (e.g. radiation detector, well counter, dose calibrator). The radiation physicist should also be familiar with the use of specialized hardware and software to analyze data in the context of internal dosimetry.

The nuclear medicine physician contacts and involves the medical physicist for the therapy planning. In consultation with the medical physicist, prior to the therapy, and on an individual basis, it is checked whether or not the internal radiation dose for the patient will be determined before or during therapy. The advice of the medical physicist is added to the patient record. The medical physicist needs to be notified if there is a deviation from the treatment protocol. The medical physicist should maintain his/her knowledge about basic and advanced techniques for internal dosimetry in nuclear medicine.

Appendix 2. Physical properties of considered radionuclides

Radionuclide	**Y-90**	**Lu-177**
Physical half-life	64.1 hours	6.7 days
Emissions for imaging	Bremsstrahlung and positron emission[4]	Gamma rays
Max. energy beta-minus	2.28 MeV	498 keV
Max. particle range in tissue	11 mm	2 mm
Mean energy beta-minus	933 keV	133 keV
Mean particle range in tissue	4 mm	0.2 mm
Energy gamma rays		113 keV (6%) 208 keV (11%)

7. RECOMMENDATIONS FOR FURTHER RESEARCH

Given the relative lack of clinical data with the highest level of evidence for this treatment, the groups who will be involved in developing it are strongly encouraged to share data and exchange ideas as often as possible. Further, to the extent of the possible, clinical trials with independent funding should be carried out and data recorded and reported to the scientific community.

[4] The 0.003 % internal pair production branching ratio of ^{90}Y allows for a very low, but measurable, positron abundance that can be used for PET scanning (Lhommel, 2010).

8. COMPOSITION OF THE WORKING GROUP

All experts joined the working group ***in a private capacity.*** The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

The following experts were involved in drawing up the advice:

Name	Expertise	Affiliation
BAETE Kristof	Medical Physics	UZ Leuven,KU Leuven[5]
BORBATH Ivan	Oncological Gastroenterology	UCL
CAVELIERS Vicky*	Radiopharmaceutics	UZ Brussel, VUB
DE GEEST Ellen	Medical Physics and Radiation protection	AV Controlatom
DE VOS Filip*	Radiopharmaceutics	UGent
DE SPIEGELEER Michel	Radiation Protection	UCL
HUSTINX Roland	Nuclear Medicine	CHU, Ulg
JAMAR François*	Nuclear Medicine	UCL
LAMBERT Bieke	Nuclear Medicine	UGent
PAULUS Patrick*	Nuclear Medicine	Hôpital de la Citadelle, Liège

The administration was represented by:

VANDECAPELLE Marleen, Federal Agency for Nuclear Control (FANC)

The following individuals were heard:

Name	Expertise	Affiliation
DEROOSE Christophe	Nuclear Medicine	KULeuven
HENDLISZ Alain	Gastroenterology	Institut Jules Bordet

The following external reviewer was heard:

Name	Expertise	Affiliation
KWEKKEBOOM Dik	Nuclear Medicine	Erasmus MC

The working group was chaired by François JAMAR, the scientific secretary was Veerle MERTENS.

[5] K. Baete is responsible for the Medical Physics in the Department of Nuclear Medicine at the UZ Leuven; as agreed upon initially, his input to the final report was limited to the dosimetry aspects, and not to discussion of other (restrictive) conditions for use.

About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send an e-mail to info.hgr-css@health.belgium.be

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