ANSES Opinion
Request No 2017-SA-0229

The Director General

Maisons-Alfort, 10 July 2019

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the possible health effects associated with high specific absorption rate values from mobile telephones carried close to the body

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It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 10 July 2019 shall prevail.

On 30 October 2017, ANSES received a formal request from the Directorate General for Risk Prevention (DGPR) and the Directorate General for Health (DGS) to undertake the following expert appraisal: "Request for scientific and technical support on characterisation of actual population exposure to emissions from radio equipment used close to the body and on development of an exposure indicator".

In this formal request, ANSES was asked to indicate whether specific absorption rate (SAR) values exceeding 2 W/kg, such as those recorded by the French National Frequency Agency (ANFR) in measurements taken between 2012 and 2016 on radio equipment in contact with the body, are liable to cause health effects, while distinguishing between adult and child populations.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Between 1 January 2012 and 31 December 2016, 379 mobile telephones underwent SAR[1] compliance checks by the ANFR. "Trunk SAR" measurements, corresponding to use of a telephone carried close to the torso, such as in a jacket pocket or a bag, were carried out on 280 of these mobile telephones in accordance with the requirements of product standard EN 50566 under European Directive 1999/05/EC of 9 March 1999, known as the "R&TTE" Directive, which was in force at the time. This stipulated that manufacturers could choose a distance of between 0 and 25 mm between the body and the device to be tested, in order to measure the trunk SAR[2]. For the

[1] The specific absorption rate (SAR) is the amount of electromagnetic energy per unit of time and mass dissipated in the body's tissues.

[2] Head SAR is measured in different configurations, in which there is at least one contact point between the head and the device (see standard NF EN 62209-1).

tested telephones, the distances chosen by the manufacturers varied between 5 and 25 mm, with the vast majority at 15 mm. In these conditions, there were no recorded cases of the exposure limit value of 2 W/kg, defined by the Ministerial Order of 8 October 2003 laying down technical specifications for radio terminal equipment, being exceeded.

However, the ways in which mobile telephone uses have developed today are reflected in a wide variety of situations in which these devices are no longer positioned solely near the head, but are held close to or in contact with the trunk, without the restrictive conditions of use in terms of distance from the body defined by the manufacturers necessarily being applied on a routine basis.

In this regard, between 2012 and 2016, the ANFR carried out additional trunk SAR measurements at distances of 0 mm and 5 mm from the body. These measurements, which were not constrained by the distances stipulated by the manufacturers, were outside the normative framework. However, they were representative of certain realistic exposure situations, and they identified trunk SARs above 2 W/kg for some mobile telephones.

At the same time, the "R&TTE" Directive, under which product standard EN 50566 gave the manufacturer itself the opportunity to define the trunk SAR measurement distance, was repealed by Directive 2014/53/EU of 16 April 2014 on the harmonisation of the laws of the Member States relating to the making available on the market of radio equipment (known as the Radio Equipment Directive, or "RED"). In particular, this Directive stipulates that SAR measurements now have to take into account "reasonably foreseeable" distances of use.

The "RED" entered into force on 11 June 2014, and has been applicable in Europe since 13 June 2016. During a one-year transitional period (from 13 June 2016 to 12 June 2017), both Directives (either "R&TTE" or "RED") were applicable. Therefore, equipment placed on the market under the “R&TTE” Directive according to conditions of use "foreseen by the manufacturer" (i.e. at a distance of 0 to 25 mm from the body), some of which had SAR values measured in contact with the body of more than 2 W/kg, continued to be marketed until June 2017. Because a telephone is used on average for several years (3-5 years), a number of these telephones are probably still in use today.

In this context, the Director General for Risk Prevention and the Director General for Health made a formal request to ANSES to find out whether trunk SAR values above 2 W/kg, such as those recorded by the ANFR between 2012 and 2016 when measuring radio equipment in contact with the body, are liable to cause health effects.

Furthermore, based on the ANSES Opinion on "Exposure to radiofrequencies and children's health" published in June 2016, it appears that "children may be more exposed than adults because of their morphological and anatomical features and the nature of their tissues". ANSES was therefore asked to distinguish between adults and children in this expert appraisal.

2. ORGANISATION OF THE EXPERT APPRAISAL

2.1. Collective expert appraisal

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

The expert appraisal falls within the sphere of competence of the Expert Committee (CES) on "Assessment of the risks related to physical agents, new technologies and development areas". ANSES entrusted the expert appraisal to external expert rapporteurs. The methodological and scientific aspects of the work were presented to the CES on "Assessment of the risks related to physical agents, new technologies and development areas" between 15 February 2018 and 17 April 2019. They were adopted by the CES on "Assessment of the risks related to physical agents, new technologies and development areas" during its meeting on 21 June 2019.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

2.2. Methodology

The expert appraisal was conducted on the basis of the publications identified and analysed in the Agency's most recent reports on the risks associated with radiofrequencies emitted in particular by mobile telephones (ANSES 2009, ANSES 2013 and ANSES 2016), and supplemented by a review of the more recently published literature on the subject (until early November 2018).

Seven expert rapporteurs, some of whom were members of the CES on "Assessment of the risks related to physical agents, new technologies and development areas", were asked to support ANSES in this work, on the basis of their skills in the areas of health risk assessment, biology and physics of electromagnetic radiation.

2.2.1. Literature review

Bibliography from the most recent reports on the subject produced by ANSES

Experimental studies that exposed animals *in vivo* or cells *in vitro* to SARs above 2 W/kg were extracted from all the literature reviewed in the "radiofrequencies and health" reports published in 2009 (AFSSET 2009), in 2013 (ANSES 2013) and in the "Exposure to radiofrequencies and children's health" report published in 2016 (ANSES 2016). Studies that were found to be of inadequate quality following the experts' analysis were not used. Thus, 62 publications on SARs above 2 W/kg were extracted from the 2009 report, and 32 from the 2013 report. A total of 20 studies concerning SARs above 2 W/kg were also identified in the 2016 report. However, they all corresponded to studies from the 2009 and 2013 reports, and the more recent studies included in the 2016 report only concerned SARs below 2 W/kg.

Identification of the more recently published literature on the subject

The ANSES coordination team and the expert rapporteurs carried out a literature search by querying search engines and databases specifically identifying studies in the area of health and electromagnetic fields (*Scopus* and *EMF-Portal*). The bibliography of the most recent report covering both adult and child populations (ANSES 2013) ends in December 2012. The objective of the literature search was therefore to identify original articles published between 1 January 2013 and 6 November 2018, the end date of the literature data collection. Due to time constraints, articles were selected directly from a reading of the abstracts. The purpose was to establish whether SAR values above 2 W/kg were liable to cause health effects. Publications were therefore selected if the SAR value was specified in the abstract and was above 2.0 W/kg, and if a biological or health effect was investigated in relation to this exposure. If the SAR was not mentioned in the abstract, the article was not selected. This led to 53 articles being identified for inclusion in the expert appraisal.

In addition, four original articles published in peer-reviewed scientific journals but not identified from the literature search were added to the selected panel of studies by the expert rapporteurs.

A total of 57 articles contributing to the assessment of evidence of possible health effects were therefore obtained.

Additional data

The final report of the US National Toxicology Program (NTP) was released online on 1 November 2018. It concerns the results of experimental studies on the effects of high SAR radiofrequency electromagnetic waves (up to 10 W/kg for lifetime exposure) in rats and mice. The draft report published in February 2018 was the subject of an ANSES opinion (ANSES 2018). In the final report, as compared to the draft report, only the levels of evidence of radiofrequency carcinogenicity were

reviewed, the results of the studies did not change. The NTP's final report was therefore selected by the expert rapporteurs in order to document the potential carcinogenicity of exposure to SARs above 2 W/kg, in addition to the available literature. The results of this study will not be published in a peer-reviewed scientific journal but, in accordance with NTP procedures, they have been reviewed by external experts. They were therefore included in the expert appraisal.

2.2.2. Analysis of the articles

Each study was analysed by two experts, a physicist for the part of the study concerning the exposure protocol, and a biologist for the part on the biological or health effects. Each expert reviewer completed an analysis grid with the support of the ANSES scientific coordinator. The quality of the study, i.e. the relevance and rigour of its protocol and the analysis of the results by the authors, determined its inclusion in the assessment of the evidence.

2.3. Method of assessing evidence

All the identified studies had been performed *in vitro* on cell models, or *in vivo* on rodent models (rats and mice). Only one human study was conducted with exposure to SARs above 2 W/kg, but this was not selected due to major methodological limitations. It is understandable that no other studies were carried out in humans, precisely because the regulatory exposure limit value for trunk SAR is set at 2 W/kg. Classification of evidence on the potential biological or health effects associated with exposure to high SARs was therefore mainly based on *in vivo* experimental studies (rat or mouse models), possibly supplemented by *in vitro* studies (cell cultures). The evidence classification methodology was based on the Agency's previous work, especially that for the "Exposure to radiofrequencies and children's health" report published in 2016 (ANSES 2016).

3. ANALYSIS AND CONCLUSIONS OF THE CES

3.1. Exposure limit values

3.1.1. Origin of the exposure limit values and exposure indicators

In France, as in most European countries, regulatory limit values for exposure to electromagnetic fields have been set in accordance with the European Union's 1999 recommendations (Recommendation 1999/519/EC[3]). These limit values are taken from those defined by the International Commission on Non-Ionising Radiation Protection (ICNIRP), on the basis of a search for proven health effects (ICNIRP 1998).

The ICNIRP is a non-governmental organisation officially recognised by the World Health Organisation (WHO) in the field of non-ionising radiation. It makes recommendations regarding exposure to electromagnetic fields in order to protect the public and workers from their potential health effects (ANSES 2016). The ICNIRP has begun updating its guidelines on radiofrequency electromagnetic fields, a draft of which was submitted for public consultation in the summer of 2018 (ICNIRP 2018).

SAR is an exposure indicator used for electromagnetic radiation with a frequency between about 100 kHz and 10 GHz. It represents the amount of electromagnetic energy absorbed per unit mass of tissue resulting in an increase in temperature. It is expressed in Watts per kg (W/kg). At and above around 10 GHz, the absorption of electromagnetic energy is limited to the surface layers of the skin. At these high frequencies, another exposure indicator is then used to quantify the interactions with the body: the surface power density expressed in Watts per square metre (W/m²).

[3] 1999/519/EC: Council Recommendation of 12 July 1999 on the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz).

When the SAR associated with exposure to an electromagnetic field is averaged for the whole body (human, animal), it is referred to as "whole-body SAR", which then means determining the amount of energy absorbed by the entire body. When measuring exposure to a mobile telephone, given the proximity of the device to the human body, exposure is very localised. It is then necessary to measure not the average over the whole body, but the SAR in specific locations. Three types of SARs are defined: the "head SAR", which reflects use of the telephone next to the ear, in conversation, the "trunk SAR" associated with uses where the telephone is carried close to the torso, and the "limb SAR", which corresponds to use of the telephone pressed against a member, such as when it is held in the hand or carried in an armband or trouser pocket.

The SAR limit values proposed by the ICNIRP are 2 W/kg for the head and trunk, 4 W/kg for limbs and 0.08 W/kg for the whole body.

3.1.2. Standardized SAR measurements

In the European Union, the entities responsible for placing mobile telephones on the market must compile a dossier to prove that they meet the essential requirements defined by the EU directives in force. Compliance with the SAR limit values was required by Directive 1999/05/EC known as the "R&TTE" Directive (until 12 June 2017) and then by Directive 2014/53/EU (the "RED"). To verify compliance, manufacturers commission accredited laboratories to carry out local standardized SAR measurements.
SAR values cannot be measured directly in human tissues. They are therefore assessed in the laboratory on dummies filled with liquids or gels whose electromagnetic field absorption properties, similar to those of the human body, tend to maximise exposure. The technical standards defining the compliance verification procedures recommend "averaging the local SAR" over a reference mass. In practice, this average is achieved by applying the SAR to a 10 g (in Europe) or 1 g (in the United States) cube of contiguous tissues. In addition, the technical standards require the device being tested to emit at maximum power throughout the test period, i.e. under "worst case" exposure conditions. Several measurement configurations need to be deployed: the telephone placed against the head (on the right, on the left, glued to the cheek, ear, etc.) or the trunk, at several frequencies, for all possible frequency bands and services. The maximum value obtained for all these configurations is the standardized SAR value mentioned by the manufacturers. Since 25 April 2016, in France, with the amendment of product standard EN 50566:2013, all mobile telephones whose marketing application is submitted after that date must have the trunk SAR measured with the device placed at a maximum distance from the body of 5 mm, instead of 25 mm previously.

3.1.3. SAR values measured in contact with the body

<u>Measurements carried out by the ANFR between 2012 and 2016</u>

The ANFR, a public administrative institution, is responsible for monitoring the radio and terminal equipment market, pursuant to Article R. 20-44-11 of the French Postal and Electronic Communications Code (CPCE).

The "R&TTE" Directive, which was in force during this period, stipulated that the normative trunk SAR could be measured at a distance from the trunk set by the manufacturers of between 0 and 25 mm. At the request of the ANFR, and for information purposes, additional measurements in contact with the trunk were carried out by accredited laboratories. The aim was to take account of the new ways in which mobile telephones were being used. Between 1 January 2012 and 31 December 2016, therefore, 272 mobile telephones were assessed at a distance of 0 mm from the trunk and 137 at a distance of 5 mm. It is important to note that these measurement dates did not necessarily correspond to the dates the products were placed on the market. Of the 272 telephones tested in contact with the body (0 mm), the median value of the maximum trunk SAR ranged from 2.0 W/kg in 2012 to 3.0 W/kg in 2013 and remained above 2.5 W/kg in subsequent years; the

maximum SAR measured was 7.42 W/kg (see Figure 1a). In this sample, 206 telephones (76%) had trunk SAR values above 2 W/kg (see Figure 1b). With the exception of 2012, more than half of the mobile telephones tested were assessed with a maximum trunk SAR value in contact with the body above 2 W/kg (see Figure 1b).

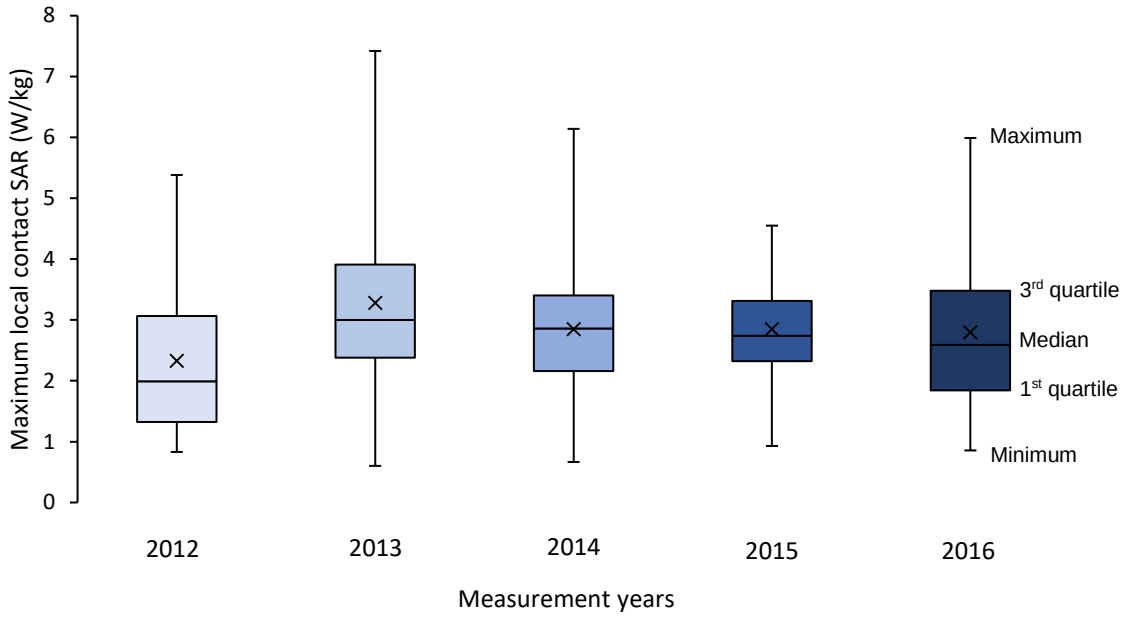

Figure 1a: Boxplots representing the distribution (minimum, 1st quartile, median, 3rd quartile, maximum) and mean (x) values of the maximum local trunk SAR of mobile telephones tested by the ANFR in contact with the body between 2012 and 2016 (measurement years). Source: ANFR

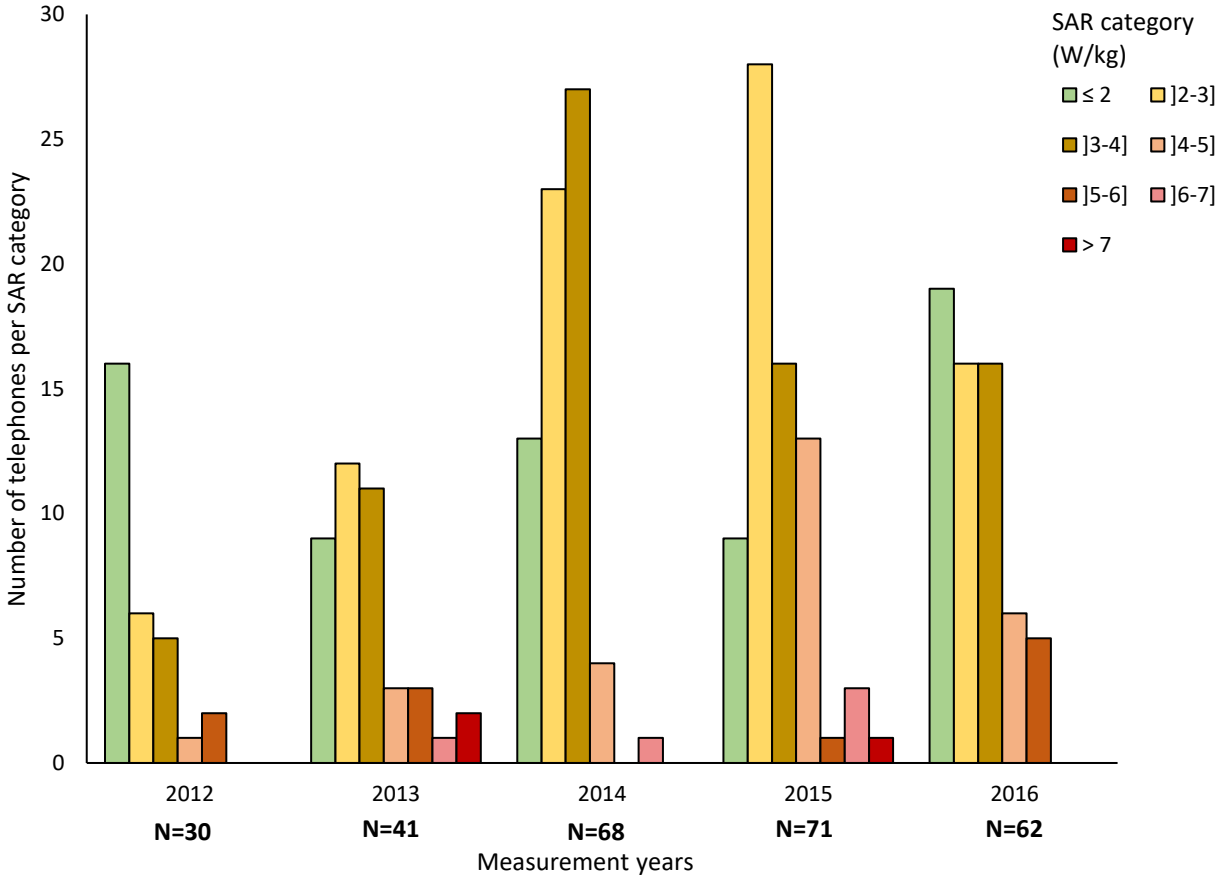

Figure 1b: Number of mobile telephones by SAR values measured in contact with the body by the ANFR between 2012 and 2016 (measurement years) and total number of telephones tested per year (N). Source: ANFR

In addition, of the 137 telephones tested at 5 mm, 18 had trunk SAR values above 2 W/kg and the maximum SAR measured was 3.65 W/kg.

Tests carried out by the ANFR in 2017 and 2018

Since 25 April 2016, with the amendment of product standard EN 50566:2013, the normalised measurements for tests of trunk SAR have been carried out at a distance of no more than 5 mm. They are published by the ANFR every six months.

In 2017, the ANFR tested the trunk SAR of 69 telephones from 29 different brands according to the conditions of product standard EN 50566. For the vast majority of telephones tested (60 out of 69), the measurement was carried out at a distance of 5 mm or less, in accordance with the regulations that came into force on 25 April 2016, pursuant to Directive 2014/53/EU, known as the "RED". However, some of the telephones tested in 2017 had a certification date prior to 25 April 2016 and were therefore tested in accordance with the regulations applicable when they were placed on the market: three telephones were tested at 10 mm, five at 15 mm and one at 25 mm. Of the 69 telephones tested, the median trunk SAR value was 1.23 W/kg and seven telephones exceeded the limit of 2 W/kg. The maximum measured value was 2.5 W/kg.
In the seven cases of non-compliance, the entities responsible for placing the product on the market were given notice by the ANFR to take the necessary measures to bring the offending product into compliance. For two of these telephones, namely the Orange HAPI 30 and the TP-Link NEFFOS X1 TP902A, the decision was made to withdraw the product from the market and recall those already sold. For the other five telephones (Alcatel PIXI 4-6" (9001D), Huawei HONOR 8 (FRD-L09), Hisense

F23, Echo STAR PLUS and Wiko TOMMY2), the telephone software was updated to bring them into compliance. The ANFR then systematically monitored the effectiveness of the solutions implemented.

3.1.4. Animal studies and measurement of SAR

In animal studies, exposure is measured either by considering an averaged SAR for the entire body, referred to in studies as "whole-body SAR", or an averaged SAR in a 10 g cube in the head, referred to in studies as "head SAR". Accordingly, although the formal request concerns "trunk SAR" values, reflecting the use of telephones in contact with the torso, "averaged SAR for the entire body" and "averaged SAR in 10 g in the head" exposure types will be analysed below to answer the question about the potential health effects of exposure to SARs above 2 W/kg.

Human exposure to a mobile telephone is relatively localised, at the part of the body near which the telephone is positioned: close to the head, the limbs and, in the context of this expert appraisal, near the trunk. Several organs can therefore potentially be exposed in addition to the skin: heart, digestive system, reproductive system, etc.

In small animals such as rodents, exposure may be local (e.g. the head), through specific exposure systems, but it is most often global, exposing the entire body. Questions could therefore be asked about the relevance of these studies to the issue addressed in this expert appraisal. Indeed, the health effects potentially observed could result from 1) an increase in the animals' overall body temperature and 2) targeted exposure of different organs or even exposure of all organs, including the brain. It is impossible to distinguish one cause from another. It is therefore important to note that animal experimental exposures are quite different from the situation of mobile telephone use by humans.

In vitro, given the small size of cell culture media, exposure is characterised by SAR averaged over a volume containing 10 g of cells and substrate.

3.2. SAR levels and thermal effects

The formal request concerns the potential effects of exposure to SARs above 2 W/kg. The studies analysed focused on a wide range of SAR values, some of which far exceeded 2 W/kg. Some studies tested several levels ranging from "low" SARs (< 2 W/kg) to higher SARs, in order to be able to study a potential dose-effect relationship.

The regulatory exposure limits of 2 W/kg were set with the aim of avoiding the thermal effects of radiofrequency exposure. This is because the only health effect of radiofrequency exposure regarded as proven by the ICNIRP in its guidelines for establishing exposure limit values published in 1998, which led to the French regulatory limit values, is tissue heating (ICNIRP, 1998). In the update to this guide, the draft of which was submitted to a public consultation in 2018, this effect was still the only one considered by the ICNIRP to be proven (ICNIRP 2018). For exposure below the limit values, this heating phenomenon is limited due to the body's thermoregulatory abilities. However, with long periods of exposure and in particular at sufficiently high intensities, the energy provided by the radiofrequencies can produce a temperature increase in the exposed tissues of sufficient magnitude to exceed the body's thermoregulatory abilities and thus disrupt its functioning.

Transposition of the experimental data available in animals shows that exposure of humans at rest to a whole-body SAR of between 1 and 4 W/kg for about 30 min may result in an increase in body temperature of less than 1°C, thus not exceeding the body's thermoregulatory abilities (ICNIRP, 1998). Exposure to more intense fields, leading to SAR values exceeding 4 W/kg, can lead to deleterious effects associated with tissue heating. In rats, experimental data indicate that thermoregulatory abilities are not exceeded when the animals are exposed to SARs below 4 W/kg

(ICNIRP, 1998). An NTP study showed that the body temperature of animals exposed to 6 W/kg does not increase; however, they are probably experiencing "thermal discomfort" that could have physiological consequences. At higher exposure intensities (around 9 W/kg and above), the thermal effects appear to be more obvious, as the animals' thermoregulatory abilities are overwhelmed. In these cases, biological and health effects secondary to the temperature increase can be expected.

It should be noted that rats do not have the same thermal response to radiofrequency exposure as humans. In particular, the level of temperature rise (lower peak temperature in humans for similar exposure) and its change over time are different, especially in deep tissues such as the brain (Kodera and Hirata 2018). In addition, for *in vitro* experiments, it should be noted that cells do not have the thermoregulatory abilities available to a complete organism. Since the threshold for thermal effects may be lower in a cell culture than in a complete organism (*in vivo*), thermal effects may be observed *in vitro* if a temperature regulation system has not been combined with the exposure system.

Although the generation of thermal effects in biological tissues through exposure to radiofrequencies is now well understood, current questions mainly focus on the possibility that radiofrequencies may cause "non-thermal" effects that could occur at lower levels of exposure. A "non-thermal" effect is defined as a biological change that occurs when the increase in body temperature is less than 1°C (IARC 2013). Below the exposure levels involving thermoregulation, two types of biological – and possibly health – effects can be considered. The first may be related to mechanisms of interaction between electromagnetic fields and living organisms that do not involve a conversion of electromagnetic energy into thermal energy. To date, no such mechanism has been clearly identified, but examples include the effects observed on the increase in electroencephalogram (EEG) spectral power in the sleep spindle frequency range following exposure of humans to electromagnetic fields during sleep. The second may be directly or indirectly related to the conversion of electromagnetic energy into thermal energy, without however the body being compelled to trigger an overall thermoregulatory mechanism (ANSES 2013).

3.3. Summary of the potential effects of exposure to devices emitting SARs > 2 W/kg

In the framework of this expert appraisal, no distinction was made between effects observed within or beyond the body's thermoregulatory abilities, considering that this is an effect associated with exposure to radiofrequencies, whether or not it occurs secondary to a temperature increase.

3.3.1. Effects on the nervous system and cognitive functions

Summary of the results of the available studies

Regarding the seven blood-brain barrier (BBB) studies, six showed no effect of radiofrequency exposure at SARs above 2 W/kg in adult or juvenile animals. The seventh reported an increase in permeability after chronic exposure (4 weeks) of adult rats to a SAR of 13 W/kg. It should be noted that in the same study, acute exposure of young rats to a SAR of 13 W/kg did not affect the permeability of the BBB.

The studies on cellular responses in the brain included the analysis of effects *in vivo* in young or adult animals or *in vitro* on neuron numbers and morphology (11 studies), synaptic activity and brain plasticity (10 studies), oxidative stress (two studies), abundance of heat shock proteins (three studies), autophagy (three studies) and neuroinflammatory response (16 studies). The analysed studies gave heterogeneous results: negative effects were reported in six of 12 *in vitro* studies (human or animal [mainly rat and mouse] cell lines) and in 20 of 36 *in vivo* animal studies, with SARs ranging from 3.3 to 19 W/kg.

The effect of exposure on cognitive function was studied in rats or mice, including the effect on learning and spatial or emotional memory, in both adults and young (11 studies). Contradictory effects were found: either positive (improvement of cognitive functions, two studies), negative

(decrease in memory performance, five studies) or reporting an absence of effect (four studies). With regard to behaviour (anxiety and locomotion), of the three studies identified, two found no effect in either young or adult animals, while the third reported a decrease in anxiety in adult and elderly rats following four weeks of exposure to a SAR of 6 W/kg.

The four studies on neuronal electrical activity at rest all reported fluctuations in this activity following exposure to SARs in the range of 3 and 15 W/kg. These fluctuations resulted *in vivo,* in adult rats or mice or young rats, in modulation of the EEG signal and *in vitro,* in modulation of electrophysiological recordings during or immediately after exposure.

The only neurodegenerative disease examined in the analysed studies was Alzheimer's disease. The results of the three *in vivo* experimental studies (transgenic mice carrying five human mutations) converged to show a beneficial effect of radiofrequencies for a SAR of 5 or 6 W/kg after chronic exposure of 8 months. The observed effects concerned memory, reduction in amyloid-beta peptide (the constituent of amyloid plaques, which are histopathological markers of the disease in humans) and in neuroinflammation, and increased brain metabolism. These effects were not found after exposure lasting three months. However, an *in vitro* study (human neuroblastoma cells, mouse hippocampal neurons, three days of exposure, SAR = 6 W/kg) found no significant effect on metabolism of the amyloid-beta peptide. It should be noted that the three *in vivo* studies came from the same team. Replication of these studies by other researchers would be necessary to ensure the reproducibility of the observed results.

Lastly, there are few data on potential effects on the auditory and visual systems. The four studies on the auditory system reported heterogeneous results, both *in vitro* and *in vivo*, in rats or mice. The only study on the visual system was carried out *ex vivo* and reported no radiofrequency effects for SARs up to 20 W/kg.

Assessment of the evidence on the identified effects

In adult animals

The experimental data analysed provide limited evidence to conclude that there is an effect from exposure to radiofrequencies with SARs above 2 W/kg on:

- changes in synaptic activity or brain plasticity (three out of three studies [rats]);
- neurodegenerative diseases (improvement in cognitive performance and in several markers of the disease in a transgenic mouse model) (three out of three studies [mice] from the same team);
- brain electrical activity resulting in modulation of the EEG signal *in vivo* or in modulation of electrophysiological recordings *in vitro* during or immediately after exposure (two out of two studies [rats or mice]).

It is not possible to conclude from the data currently available whether or not there is an effect from exposure to radiofrequencies with SARs above 2 W/kg on:

- the blood-brain barrier (five studies [rats or mice], only one of which reported a deleterious effect);
- cell viability or neuron morphology (three studies [rats or mice], only one of which showed a deleterious effect);
- neuroinflammation in conditions of a pre-existing inflammatory disorder (1 study [rats]);
- cognitive functions, memory and behaviour in healthy animals (six studies [rats or mice] with contradictory results);
- auditory function (1 study [rats]).

The experimental data analysed provide evidence in favour of no effect from exposure to radiofrequencies with SARs above 2 W/kg on neuroinflammation in healthy animals (three out of three studies [rats or mice]).

In vivo data in adult animals are non-existent with respect to:

- autophagy, oxidative stress and abundance of thermal shock proteins;
- the visual system.

In young animals

The data currently available provide limited evidence to conclude that there is an effect from exposure to radiofrequencies with SARs above 2 W/kg on the induction of autophagic processes in the brain (three out of three studies [mice]).

It is not possible to conclude from the data currently available whether or not there is an effect from exposure to radiofrequencies with SARs above 2 W/kg on:

- cell viability or neuron morphology (three studies [rats or mice] with contradictory results);
- synaptic activity, brain plasticity and calcium (five studies [rats or mice] with contradictory results);
- neuroinflammation (11 studies [rats or mice] with contradictory results);
- brain electrical activity (one study [rats]);
- cognitive functions, memory and behaviour (six studies [rats] with contradictory results);
- auditory function (1 study [mice]).

The experimental data analysed were in favour of no effect from exposure to radiofrequencies with SARs above 2 W/kg on:

- the blood-brain barrier (five out of five studies [rats or mice]);
- thermal shock proteins (three out of three studies [rats or mice]).

In vivo data in young animals are non-existent with respect to:

- oxidative stress;
- the visual system.

3.3.2. Carcinogenic effects

Summary of the results of the available studies

The analysis of the 21 studies investigating the potential genotoxic effect of radiofrequencies (chemical modification of DNA, chromosome breaks and abnormalities, induced mutations) revealed that the majority of studies did not show any effect for SARs ranging from 0.4 to 33.2 W/kg, whether *in vitro* on various types of human or mouse cells (11 studies), or *in vivo* in adult mice (two studies). On the other hand, five *in vitro* studies reported an increase in DNA damage or chromosomal abnormalities for SARs of 3 or 4 W/kg but not for lower SARs, suggesting a possible dose-dependent effect.

Radiofrequency co-genotoxicity has also been examined in various *in vitro* studies, most of which agree that radiofrequencies may potentiate DNA damage induced in various cell types (human, mouse or hamster) by known chemical or physical mutagens (such as UVA), with SARs ranging from 3 to 200 W/kg (eight out of 10 studies). However, *in vivo* studies in animals for SARs above 2 W/kg are non-existent.

With regard to effects on the development of tumours *in vivo*, the results of all 10 studies identified in adult animals were consistent and did not provide evidence of any increase in the incidence or aggravation of various types of tumours (mammary, lymphoma, lung, liver, uterus, adrenal gland, pituitary gland) in rats or mice exposed to whole-body SARs of 0.4 to 4 W/kg or on the formation or development of glial tumours in mice after subcutaneous inoculation of astrocytes or glioma cells previously exposed to a SAR of 5 W/kg. However, for exposure occurring from the *in utero* development phase or from early development and continuing throughout the animal's lifetime, the results of the two studies identified are inconsistent: one reported no effect on lymphoma development for exposure to whole-body SARs of 4 W/kg, while the National Toxicology Program

(United States) found a significant increase in the incidence of cardiac schwannomas in male rats exposed to 6 W/kg for two years, with a dose-response relationship, and a significant increase in lymphoma incidence in female mice exposed to a whole-body SAR of 2.5 W/kg only. It should be noted, however, that these results are difficult to interpret due to shorter survival times in control animals and late onset of cancer in exposed animals.

Assessment of the evidence on the identified effects

In adult animals

It is not possible to conclude from the data currently available whether or not there is a genotoxic effect from exposure to radiofrequencies with SARs above 2 W/kg (two out of two *in vivo* studies [mice] showing no effect).

The experimental data analysed provide evidence in favour of no effect from exposure to radiofrequencies with SARs above 2 W/kg on the development of tumours *in vivo* (seven out of seven studies [rats or mice]).

In vivo data on co-genotoxicity are non-existent, which makes it impossible to reach any conclusions. It seems important to carry out such studies in animals in view of the consistent *in vitro* data in favour of potentiating effects (eight out of 10 studies).

In animals with lifetime exposure from early development

It is not possible to conclude from the data currently available whether or not there is an effect from exposure to radiofrequencies with SARs above 2 W/kg on the development of tumours *in vivo* (one out of two studies [rats and mice] showing an effect but with methodological limitations).

Data on genotoxicity or co-genotoxicity in young animals are non-existent.

3.3.3. Other non-carcinogenic effects

Summary of the results of the available studies

The analysis of studies on other effects, apart from carcinogenic effects, revealed contradictory results *in vitro* on different types of human or animal cells (embryonic, glioblastoma, breast cancer, auditory or immune system, and blood) (10 studies reporting no effect and nine reporting a deleterious effect). No radiofrequency effects on gene expression and protein abundance with SARs above 2 W/kg were observed *in vivo* in the brain or skin of adult animals (three out of three studies). However, in juvenile animals, a potential effect cannot be ruled out: the only study identified reported a variation in gene expression or protein abundance *in vivo* in the brain.

With respect to reproduction, effects on the male reproductive system were observed *in vitro,* but not *in vivo* in rats; studies are non-existent in male mice. In females, of the two studies analysed in rats, the first did not show any effect while the second reported deleterious effects on the reproductive system. However, the SAR value was very imprecise (ranging from 0.016 to 4 W/kg).

With regard to development in young animals (rats and mice), the results of the three studies identified on the *in utero* or postnatal period converge to show no effect (malformations, birth weight, lethality, clinical signs) for exposure of the mother or newborn to a whole-body SAR of 4 W/kg.

With regard to the immune system, the four *in vitro* and *in vivo* studies in young animals (rats or mice) were in favour of no effect. There are no studies on the subject in adult animals.

Lastly, two studies on the endocrine system (thyroid, stress and sex hormones, melatonin) were identified. They converge towards no effect in adult animals, but have only been performed in rats. There are no studies on the subject in young animals.

Assessment of the evidence on the identified effects

In adult animals

It is not possible to conclude from the data currently available whether or not there is an effect from exposure to radiofrequencies with SARs above 2 W/kg on:

- the female reproductive system (two studies with contradictory results [rats]);
- the endocrine system (two studies reporting no effect [rats]).

The experimental data analysed provide evidence in favour of no effect from exposure to radiofrequencies with SARs above 2 W/kg on gene expression and protein abundance (three out of three studies [rats and mice]).

In vivo data in adult animals are non-existent with respect to:

- the immune system;
- the male reproductive system.

In young animals

It is not possible to conclude from the data currently available whether or not there is an effect from exposure to radiofrequencies with SARs above 2 W/kg on gene expression and protein abundance in the brain (one study [rats]).

The experimental data analysed were in favour of no effect on:

- *in utero* or postnatal development (five out of five studies [rats and mice]);
- the immune system (four out of four studies [rats and mice]).

In vivo data in young animals are non-existent for the endocrine system.

3.4. CES conclusion and recommendations

3.4.1. Conclusion on the potential health effects of exposure to SARs above 2 W/kg

This assessment of the health effects of radiofrequencies needs to be integrated into a more global approach, mainly taking into account the results observed at SAR levels below 2 W/kg. It should be pointed out that some studies considering SARs below 2 W/kg have reported biological effects (see the reports by AFSSET 2009, ANSES 2013 and 2016).

In this expert appraisal, several of the identified studies analysed different levels of exposure, below and above 2 W/kg. The majority of these studies did not report any difference in effect between a SAR below and above 2 W/kg. This was the case for the *in vitro* studies (from 0.1 to 10 W/kg) and *in vivo* studies showing no effect: they concerned the blood-brain barrier (six out of seven studies), neuron numbers, morphology and cell death (one out of two studies), brain plasticity and calcium (two out of four studies), the abundance of thermal shock proteins and autophagy (two out of two studies), the immune system (three out of three studies), genotoxic effects (two out of two studies) or the development of *in vivo* tumours (five out of seven studies). On the other hand, several *in vivo* studies reported SAR-dependent effects and highlighted effects that appear specifically from exposure levels above 2 W/kg. This was particularly the case for neuroinflammation (three out of six studies), memory (four out of six studies) and gene expression and protein abundance (six out of 14 studies). However, it should be noted that the highest exposure levels implemented in the analysed studies are unlikely to be encountered when using the mobile telephones available on the market, and that users are therefore not exposed to them. Indeed, the actual level of user exposure at any given moment depends largely on the reception conditions (adaptation of the transmitted power) and the network used (2G, 3G, 4G, etc.). On average, over the duration of a telephone conversation, the normative SAR value as measured in the laboratory under maximising conditions represents a "worst case" exposure situation, which should in practice never be reached. In addition, in animals, the

exposures reported in this formal request most often involved the entire body, a situation that does not occur in humans at such exposure levels.

3.4.2. Recommendations concerning the reduction in levels of exposure to radiofrequencies

Considering:

the results of the 2013 ANSES expert appraisal, which had highlighted:

- in animals, with limited evidence, effects on sleep, male fertility and cognitive performance (an improvement) for SARs below 2 W/kg;
- in humans, with limited evidence, an increased risk of vestibular-acoustic nerve neuroma and glioma for intensive users with more than 1640 hours of accumulated exposure to mobile telephones;
- in humans, with sufficient evidence, a short-term physiological change in brain activity during sleep;

the results of the 2016 ANSES expert appraisal, which had highlighted:

- in children, possible effects on cognitive function on the one hand and well-being on the other (although these effects on well-being may be associated with the use of the mobile telephones rather than the radiofrequencies they emit);

the results of this expert appraisal, which highlight, with limited evidence:

- in adult animals, effects on synaptic activity or brain plasticity and on brain electrical activity (modulation of the EEG signal);
- in transgenic animal models of Alzheimer's disease, an improvement in cognitive performance;
- in young animals, effects on the induction of autophagic processes in the brain;

the CES recommends that the normative trunk SAR of mobile telephones be measured with the device in contact with the body, at a distance of 0 mm, in order to reflect a maximum but realistic exposure situation.

The CES also recommends, as a precaution, that mobile telephone users should no longer be exposed to devices with a SAR exceeding 2 W/kg when measured close to the body (trunk SAR measured in contact with the body, at 0 mm).

Lastly, the CES extends these recommendations to all devices emitting radiofrequencies (tablets, toys, etc.) and liable to be used in contact with the body.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

In view of the emergence of new ways of using mobile telephones, which have led to these sources of radiofrequency electromagnetic fields being placed in the vicinity not only of the head, but also of other parts of the body, ANSES was formally asked to indicate whether SAR values exceeding 2 W/kg were liable to cause health effects, while distinguishing between adult and child populations. Indeed, in measurements carried out between 2012 and 2016 on mobile telephones in contact with the trunk, i.e. in more stringent situations than required by the standard applicable under the previous European Directive "R&TTE" (1999/5/EC), but which may be realistic, the ANFR noted a large proportion of trunk SAR values exceeding 2 W/kg and extending up to 7 W/kg.

The expert appraisal conducted by the Agency focused on identifying biological or health effects specifically associated with exposure to SARs above 2 W/kg. To this end, a review of the recent literature was conducted, in which potential biological and health effects associated with such exposure levels were studied. The data obtained came exclusively from *in vitro* or *in vivo* experimental studies in animals (with the exception of one human study that was not selected due to major methodological limitations). The methodology for assessing the level of evidence was adapted, in the absence of human studies, in order to determine the evidence from animal studies following individual analysis of the quality of publications by the expert rapporteurs. *In vitro* study data supported or qualified the levels of assessment obtained from the *in vivo* studies.

Besides the biological and health effects already reported in previous ANSES expert appraisals (mainly in 2013 and 2016), this expert appraisal points to biological effects, with limited evidence, in particular on brain activity associated with exposure above 2 W/kg. Moreover, it is not possible to conclude from the available data whether or not there is an effect on the other biological functions studied.

The Agency emphasises that the data in the scientific literature on exposure above 2 W/kg come from animal experiments for which exposure was characterised by a "head" or "whole-body" SAR. In addition, standardized SARs, such as those measured by the ANFR, are measured under conditions that maximise exposure, and which should in practice never be encountered.

The recommendations of the Expert Committee on "Assessment of the risks related to physical agents, new technologies and development areas" are based both on the results of the assessment of the evidence in this expert appraisal concerning exposure levels above 2 W/kg, and also on those of the Agency's previous expert appraisals, which considered exposure both above and below 2 W/kg (ANSES 2013, 2016).

ANSES endorses the conclusions and recommendations of its Expert Committee.

Mobile telephones placed on the market until 13 June 2016, and potentially until 12 June 2017[4], were marketed under conditions of use "foreseen by the manufacturer" (i.e. with a minimum operating distance of 0 to 25 mm from the body, away from the head). The majority of the telephones tested by the ANFR had trunk SAR values measured in contact with the body of more than 2 W/kg. Because a telephone is used on average for several years (3-5 years), a certain number of these telephones are probably still in use today.

Therefore, given that the SAR limit value (2 W/kg) was exceeded for a large proportion of telephones placed on the market under the previous European Directive (R&TTE) when used in contact with the trunk, that changing practices have led to an increasing proportion of their use being close to the body (very small or no gap between the device and the body), and uncertainties about various long-term health effects, the Agency recommends that measures be taken to ensure that users are no longer exposed to SARs exceeding 2 W/kg from telephones certified under the R&TTE Directive (those placed on the market until 13 June 2016 or even until 12 June 2017). To this end, the Agency considers that measures taken by manufacturers similar to those taken for the telephones placed on the market after 13 June 2016 and found to be non-compliant following the ANFR tests in 2017 would enable this objective to be achieved: software updates, telephone recalls, etc. Pending the implementation of such measures, the Agency invites users of these devices to comply with the operating instructions (regarding distance) mentioned by manufacturers in the instructions, when they are placed close to the trunk.

Lastly, the Agency recommends modifying the standard provisions relating to the distance of radio devices that can be placed close to the body to ensure that compliance verification measurements for SARs are carried out when the phone is in contact with the body (0 mm).

[4] The "RED" entered into force on 11 June 2014, and has been applicable in Europe since 13 June 2016. During a one-year transitional period (from 13 June 2016 to 12 June 2017), both Directives were applicable (either "R&TTE" or "RED").

Dr Roger Genet

KEYWORDS

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