Project Final Report

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1 Project Context and Objectives

1.1 Project Context

Iodine deficiency disorders (IDD) represent a global health threat to individuals and societies. The adverse effects of iodine deficiency are diverse and impose a significant burden on public healthcare systems. Adults living in iodine-deficient regions carry a high risk of goitre, thyroid nodules and hyperthyroidism. Subclinical hyperthyroidism, as a common and frequently undiagnosed IDD, is tightly associated with an increased risk of mortality and cardiometabolic diseases.

Moreover, mild-to-moderate iodine deficiency during pregnancy and breast-feeding is widespread in Europe and may adversely affect the development of the child. Due to a lack of valid data, we are uncertain about the scale of the problem but estimates suggest that up to 50% of infants in Europe are at risk of being iodine deficient. Even mild or moderate iodine deficiency of the mother has been associated with a range of adverse child neurodevelopmental outcomes, such as poorer language development and lower IQ. A marginally lower IQ in a population will weaken economic success and productivity: only a one-point decrease in IQ has been associated with a persistent 0.11% annual decrease in per-capita GDP. For years the World Health Organization (WHO) has warned that Europeans are increasingly affected by the consequences of IDD. However, Europe's IDD prevention and monitoring programmes are highly fragmented and variable, and they are widely accepted to be insufficient.

Due to fragmented monitoring programmes, there is an apparent lack of evidence about the iodine status in the European population. Therefore, it is unclear how increasing consumption of convenience food and avoidance of table salt by health-conscious people affects the iodine status. The WHO identifies an effective European monitoring programme as a crucial step towards the eradication of IDD with significant benefits for European citizens and the sustainability of health-care systems.

Current estimates suggest that 350 million Europeans are exposed to iodine deficiency, but only limited data are available about the impact on health outcomes and no evidence exist for the long-term cost effectiveness of current national prevention programmes.

IDD has not been on the political agenda in most European countries for more than a decade and progress to raise interest amongst European bodies has been slow. This is despite the fact that, with very few exceptions such as Iceland, Europe is an iodine-deficient continent.

Within the public health communities, the importance of standardisation and quality assurance in thyroid epidemiology and the importance of IDD for individual and public health need to be raised among researchers.

Public awareness of national iodine deficiency monitoring and prevention programmes is generally low, most likely due to the non-acute and not directly life threatening adverse health consequences of IDD. This results in minimal public concern about health IDD-related consequences, which needs to be addressed particularly in the light of evidence for the increased requirement for iodine in pregnant women.

1.2 Project Objectives

The overall aim of EUthyroid was to evaluate IDD prevention programmes in 27 European and associated countries and to initiate capacity building for integrated European IDD prevention and monitoring. To this end, EUthyroid implemented a collaborative project with funding by the European Union's H2020 research and innovation programme (Grant Agreement no. 634453).

To initiate the crucial steps towards the eradication of IDD in Europe, EUthyroid encompasses the following objectives:

Objective 1: Develop a European map of iodine status

For Objective 1, EUthyroid assembled a joint European database combining national/regional registry based outcome data and IDD monitoring data related to iodine status and thyroid disease. This resulted in the first valid European map of harmonised iodine status, an important milestone towards improving and harmonising legislation in Europe.

Objective 2: Build the capacity of national iodine studies to perform harmonised studies about iodine status

For Objective 2, EUthyroid promoted the harmonisation of national and regional surveys, through infrastructure of standardised socioeconomic-status questionnaires and training tools to ensure uniform interviews and ultrasound measurements. Moreover, an accredited laboratory conducted comparative measurements for thyroid related biomarkers on available biosamples from the national and regional studies. This was a considerable leap in knowledge, as previously no comparable European-wide data was available.

Objective 3: Establish thyroglobulin as a biomarker for individual iodine status

For Objective 3, EUthyroid evaluated the potential of thyroglobulin as a marker for individual iodine status through analysis of dried blood spots in the target populations: pregnant women and women of reproductive age. A dry blood spot thyroglobulin reference range for women of reproductive age could be proposed and preliminary data are promising, indicating good agreement with the international reference range for pregnant women.

Objective 4: Provide evidence for the effectiveness of IDD prevention and monitoring programmes in Europe

For Objective 4, EUthyroid performed the first analysis for cost effectiveness and long-term effectiveness of IDD prevention and monitoring programmes. In order to be able to guide decision making in the healthcare system, the project explored the long-term benefits, risks, costs, and cost effectiveness of prevention and monitoring strategies for IDD with results from a decision-analytic model developed for this project. The model was successfully developed and simulates the German population as an example European country to compare an IDD prevention programme to no prevention.

Objective 5: Disseminate EUthyroid outcomes

For Objective 5, towards the ambitious goal of disseminating project outcomes to reach policy makers and ultimately lead to policy change, EUthyroid implemented a coordinated strategy with dissemination activities tailored to actively target policy makers, stakeholders and the general public. EUthyroid's recommendations towards preventing IDD and securing sufficient iodine status in Europe, were presented in the Krakow Declaration on Iodine and garnered a tremendous response from relevant organisations, emphasising the impact of the EUthyroid project and recognising the problem within Europe. Through the actions of the integrated regional monitors from 27 countries, it was possible to target specific organisations in charge of existing IDD prevention programmes on the national and regional level, including ministries of health and health-care institutions. Several of these meetings have already led to significant policy outcomes.

In order to address these objectives EUthyroid brought together 31 partners from 27 countries, strategically incorporating IGN to bring together experts in the field of thyroid disorders. Our multidisciplinary consortium includes renowned experts from all necessary disciplines including epidemiologists, endocrinologists, clinical chemists, nutritionists, and health economists, and thus excellently positioned to achieve its major aim of initiating the crucial steps towards the eradication of IDD in Europe.

Figure 1: EUthyroid consortium © Stefanie Freynschlag

2 Overview of the results and their exploitation and dissemination

Harmonised data

During the project, the consortium successfully established a joint European database combining national and regional registry based outcome data related to iodine status from 20 European countries. Data includes incidence and prevalence of thyroid disorders and various related treatments (anti-thyroid medication, thyroid hormone replacement therapy, surgery and radio-iodine treatment). Data have been standardised to account for differences in age distribution between populations where possible and rates (raw and standardised) have been calculated. In addition, the joint European database collated data from 56 IDD monitoring studies spanning 27 European countries. Based on these monitoring studies, nationwide iodine fortification programmes can be initiated or adapted.

According to the WHO, a region is iodine sufficient if the median urinary iodine concentration (UIC) is ≥ 100 µg/L. Laboratory methods for measuring UIC, however, are heterogeneous hampering the comparability of iodine monitoring studies. Therefore, it is of utmost importance to harmonise monitoring studies to get a consistent picture of the iodine status towards Europe and beyond. EUthyroid collected urine and if available serum samples from European monitoring studies and established a central laboratory, which measured UIC using the gold-standard ICP-MS method. Cross-laboratory comparison of UIC measurements for 39 IDD monitoring studies from 23 European countries were performed to establish the first harmonised European map of iodine status in school-aged children, adults and pregnant women. This is a considerable leap in knowledge, because no comparable European-wide data were previously available.

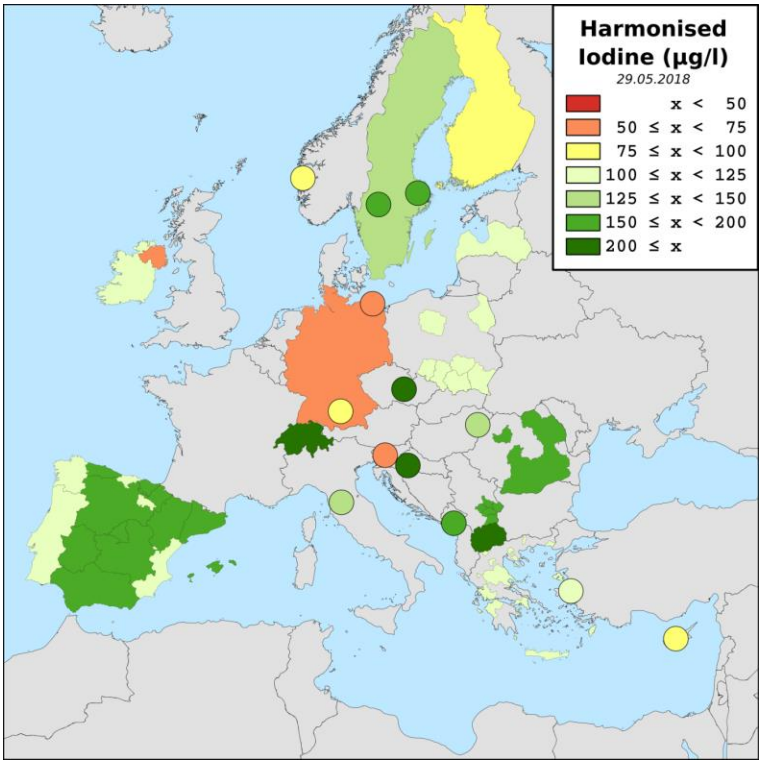

Figure 2: European map of harmonised iodine status

Of particular note, the cross-laboratory comparisons revealed major deviations compared to standardised results. The findings reiterate the importance of standardised and harmonised monitoring efforts across Europe.

To supplement the iodine status maps, measurements of serum biomarkers commonly used to define the prevalence of subclinical thyroid disorders (TSH, TPO and Tg antibodies) were depicted in additional European maps. Registry data were used to visualise thyroid disease load in maps showing the prevalence of hyperthyroidism, hypothyroidism and goitre. Data processing and statistical analyses of national/regional registry outcome data related to thyroid diseases demonstrated significant differences in registered treatment frequencies. Due to fundamental disparities among health care systems in Europe data on incident IDD and treatments a significant heterogeneity of registry data exists across countries. Moreover, availability of such registry data was incomplete for certain variables/parameters or non-existent on a national level in some countries. This severely hampered the evaluation of the success of iodine fortification programmes on the basis of diseases and related costs. EUthyroid acknowledges these limitations and calls for comparable nationwide administrative health registries as well as the use of complementary methodologies, including laboratory methods, to ensure validity of results.

Standardised studies

The EUthyroid infrastructure was established and includes a range of resources and training tools to support the harmonisation of IDD monitoring studies, including: socio-economic status (SES) questionnaires for adults and children; an instructional video on thyroid ultrasound examination, a web-based training and certification tool (ARCUS) for ultrasound observers and guides for thyroid ultrasound and researchers conducting population studies.

A SES questionnaire has been established and recommended to regional managers within the consortium. In addition to a questionnaire version suitable for adults, the EUthyroid project also established a SES questionnaire recommendation for children, acknowledging that the adult SES may not adequately represent the SES of children. Therefore, a valid and age-appropriate self-reported measure of SES in this population is inevitable. The SES questionnaires have been used in the IDD monitoring studies of four European nations, with researchers in 11 additional European countries planning on utilising the questionnaires in their upcoming respective study protocols. With respect to training tools, an instructional video on thyroid ultrasound examination, a thyroid ultrasound manual and a web-based training and certification tool (Advanced Reader Certification for Unified Studies - ARCUS) for ultrasound observers have been published. By the project' conclusion, the instructional video had accumulated more than 150 views and 11 study coordinators were registered to use the certification tool ARCUS.

Figure 3: Thyroid ultrasound guidelines

The guidance document entitled 'Guidance for researchers conducting population studies. Focus on monitoring of iodine deficiency disorders (IDD)', is one step towards harmonisation of pre-analytical factors, major sources of error, and improved quality and comparability of thyroid related human studies. The guidance document is divided into three parts. Part A includes general recommendations and issues related to study planning. Part B offers detailed instructions and recommendations for specimen collection and sample handling. Part C gives an overview of laboratory analysis related to urinary iodine and thyroid function. The guidance document has an ISBN which enables formal citation and accessibility through web searches (e.g. Google Scholar). There have been 139 registered downloads of the document so far.

Figure 4: Excerpt from the guidance document for researchers conducting population studies

All training tools are open access will remain accessible through the project´s website after the culmination of the project, encouraging further harmonisation beyond the project's consortium and lifetime.

Evaluating thyroglobulin as a biomarker for iodine status in individuals

One of the main innovative aspects within EUthyroid is the development and implementation of thyroglobulin (Tg) as a marker for the iodine status of individuals, using a field-friendly measurement technique using dried blood spots. While technically Tg can be measured, its predictive value as individual marker of iodine status required further research. The project explored the potential of dried blood spot Tg as a marker for the

individual iodine status according to WHO recommendations. The focus was on pregnant women (PW) and women of reproductive age (WRA), two key target groups for IDD prevention due to the high risk of adverse effects on their children's neuropsychological development when exposed to mild-to-moderate iodine deficiency. Additionally, within EUthyroid a dried blood spot (DBS) thyroglobulin (Tg) Enzyme-linked Immunosorbent Assay (ELISA) was developed to analyse DBS samples of PW and WRA and establish a Tg reference range. Samples from multiple IDD monitoring studies, from European and non-European studies, were collected to further cross-validate a reference range. Data of iodine sufficient countries was used to set up DBS Tg reference ranges for PW and WRA for future monitoring, as both are key target groups for ID monitoring due to their vulnerability to adverse health effects. The preliminary data for the proposed reference range for DBS-Tg for WRA indicate a good agreement with the international reference range for DBS-Tg in PW, but will require expanding with more data before it can be adopted. Both reference ranges were tested by applying them to samples of IDD monitoring studies from nine European countries, two nearby neighbour countries, and eight non-European countries for validation by checking it against urinary iodine concentration.

Around 3500 serum samples from pregnant women of two major European birth cohort studies [INfancia y Medio Ambiente (INMA) and Generation R] were analysed for Tg and Tg antibodies (TgAb). Cohort-specific differences in determinants of maternal thyroglobulin concentrations were observed. In INMA, there was a weak but significant correlation and a negative association between urinary iodine-to-creatinine ratio (UI/Creat) and thyroglobulin. Also, iodine sufficiency during pregnancy was associated with lower thyroglobulin concentrations than in women with iodine insufficiency.

Clarified mental health risks associated with low maternal iodine status

Mother-child data from three reputable European cohort studies (Generation R, Avon Longitudinal Study of Parents and Children [ALSPAC], INMA) in the Netherlands, UK and Spain were brought together, harmonised and integrated into one dataset. The dataset includes almost 9,000 pregnant women and their children. With the additional analysis of 3,000 repeated urinary iodine measurements the iodine status of pregnant women can now be classified more accurately. Moreover, it was shown that maternal thyroid function effects child neuropsychological development. Low maternal thyroid hormone (fT4) was consistently associated with lower IQ across cohorts whereas high fT4 was suggestively associated with a higher risk of autistic traits. Further studies should replicate the findings of autistic traits and investigate the potential modifying role of maternal iodine status. Overall, analysis conducted within EUthyroid confirmed T4 as a reliable marker of foetal thyroid state in early pregnancy and identified differences and

similarities in the determinants of iodine status between pregnant women from three different populations.

Optimised prevention programmes

To synthesise evidence on long-term benefits, risks, and resource utilisation of IDD prevention and monitoring programmes in Europe, a decision-analytic Markov state-transition cohort model was developed. Decision analysis was used as a systematic, explicit and quantitative approach to evaluate the long-term benefit-harm balance and cost-effectiveness of an IDD prevention programme for a moderately iodine deficient European country. The model structure was based on both published evidence and expert opinions from the EUthyroid consortium. The model simulates the incidence of IDD and disease histories of the German population as an example for a European country comparing an IDD prevention programme (iodine fortification of salt) to no prevention. A base-case analysis was conducted using a dynamic cohort approach to simulate a population reflecting the age structure and age-specific prevalence of IDDs of the currently alive population allowing for population growth due to new births. The evaluation of the dynamic population model over a time horizon of 120 years yielded total and incremental quality-adjusted life years (QALYs), total and incremental life years (LY), and total and incremental costs (EUR) for a population wide prevention programme. Cost-effectiveness was evaluated, computing the discounted incremental cost-utility ratio (ICUR, in EUR per QALY gained) and the discounted incremental cost-effectiveness ratio (ICER, in EUR per LY gained) was evaluated. Multiple deterministic one-way sensitivity analyses were conducted to evaluate the influence of different uncertain parameters on outcomes of interest. Additionally, further scenario analyses were performed, including best-case and worst-case effectiveness scenario analyses.

Dissemination of outcomes

In order to achieve the ambitious goal of disseminating project outcomes to reach policy makers across Europe and ultimately lead to policy change, a clear and coordinated strategy that incorporated all 31 project partners from 27 countries was a prerequisite for success.

For the project to generate the impact necessary it was essential that optimal external recognition of the project was generated. A distinctive corporate design (CD) was therefore developed at the start of the project and subsequently informed all project dissemination material, including the project website and social media channel.

Figure 5: EUthyroid logo ©biolution GmbH

All partners were supported by branded material for their presentations and dissemination actions to ensure that the project quickly obtained recognition amongst its stakeholder groups. The level of project recognition achieved was clearly reflected by the high number of prominent organisations who supported the Krakow Declaration on Iodine.

To ensure a unified direction for a large consortium with ambitious goals, a communication plan identifying relevant stakeholders was established in month 3 to allow for a quick and professional response to new dissemination ideas and concepts. Dissemination material was produced to address all target groups, with the corporate design even being adapted slightly for the Krakow Declaration on Iodine to incorporate larger graphic elements of particular appeal to policy makers.

The project website (www.euthyroid.eu), launched in month 4 to coincide with the kick-off meeting, formed the hub of EUthyroid's coordinated dissemination strategy to which all project dissemination was linked, including social media and partner websites, and was thus of key importance for external project recognition. The website underwent a series of major updates, significantly to incorporate the various elements of EUthyroid infrastructure as they became available and further expanded in the build-up to the Krakow Declaration on Iodine to specifically increase its impact on policy makers. A further expansion took place at the end of the project to present EUthyroid's policy and data analysis outcomes.

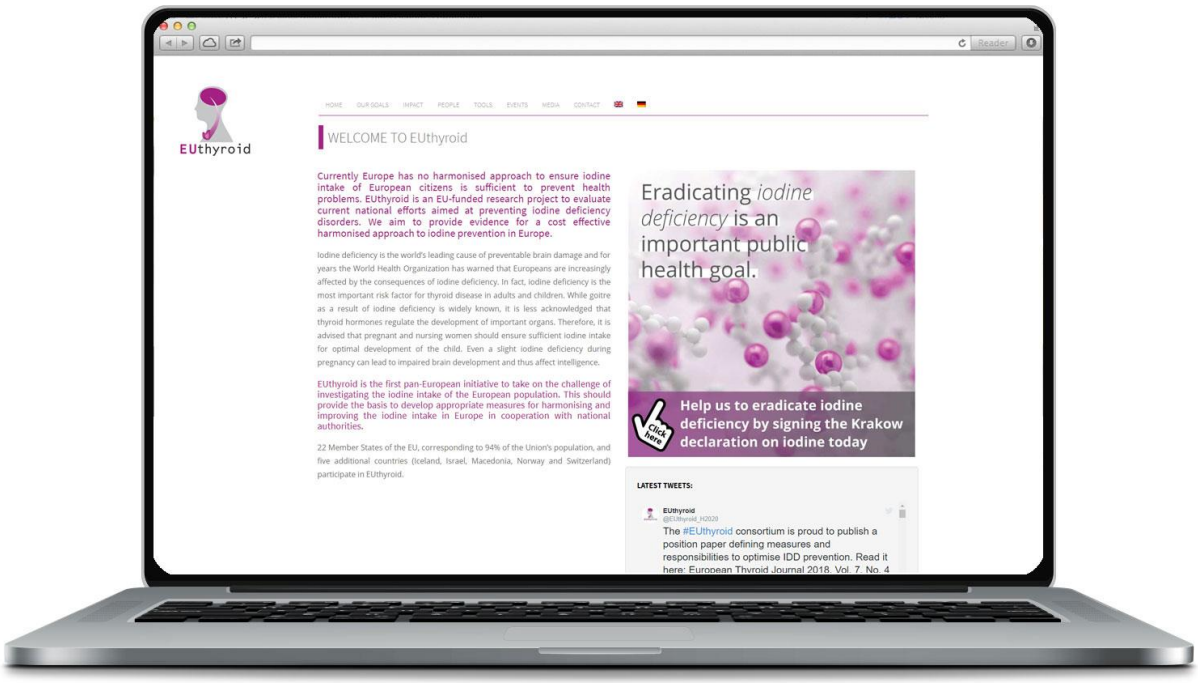

Figure 6: EUthyroid project website (www.euthyroid.eu) ©biolution GmbH

To reflect the pan-European nature of the project, a fact sheet containing all essential facts about the EUthyroid project was created in month 3 in English and German and subsequently translated into partner languages. The factsheet was made available on the project website in all 23 partner languages. The website was also partly translated into German.

Social media played an important role in the coordinated dissemination strategy, particularly as a channel to raise awareness in the public domain for the health problems associated with iodine deficiency. The EUthyroid twitter account operated in a mutual cooperation strategy with the already established IGN twitter account, together with other partners, both individual and organisations, to promote messages and ensure wide dispersal. Over the course of the project the account published 518 tweets and attracted 282 followers. Coordinated social media campaigns utilising images and animations from the EUthyroid infographic generated high exposure for the project in the period surrounding the Krakow Declaration on Iodine and generated considerable momentum both within the consortium and in the wider research and medical community. A powerful social media presence was generated capitalising on collaborations formed with multipliers in the form of influential lobby groups.

To address relevant stakeholders, partners presented EUthyroid at various conferences and public events, with further media attention generated through a kick-off press release

published in September 2015 to coincide with the EUthyroid kick-off meeting, a press release drawing attention to the EUthyroid infrastructure, distributed to various mailing lists and through the IGN network in October 2017 and a final press release for the Krakow Declaration on Iodine in April 2018.

The scientific outcomes of the project were disseminated through publication in peer-reviewed journals, presentations at scientific conferences (including two dedicated EUthyroid satellite meetings organised as pre-conference events of the 39th and 40th annual meetings of the European Thyroid Association) and on the EUthyroid website.

The major dissemination event of the project was the presentation of the Krakow Declaration on Iodine, a document outlining EUthyroid's recommendations towards preventing IDD and securing sufficient iodine status in Europe. EUthyroid presented this Declaration at a meeting in Krakow, Poland in the presence of a wide range of notable endorsees as a call to action for policy makers, public health officials, scientists and the general public.

Figure 7: Presentation of the Krakow Declaration on Iodine ©Jerzy Sawicz

The highlight of this event was a press conference where the Declaration was presented, with this accompanied by a major press release distributed widely throughout Europe by EUthyroid consortium partners and coordinated social media campaigns benefiting from the strategic inclusion of associated lobby organisations WIA, GAIN and TFI acting as

multipliers. A dedicated website was created (www.iodinedeclaration.eu), slightly adapting the corporate design to emphasise larger graphic elements designed to be attractive to policy makers. This website collected expressions of support for the declaration and alone the tremendous response from organisations confirmed that the decision to hold a declaration meeting was correct and emphasised the scope of the problem within Europe.

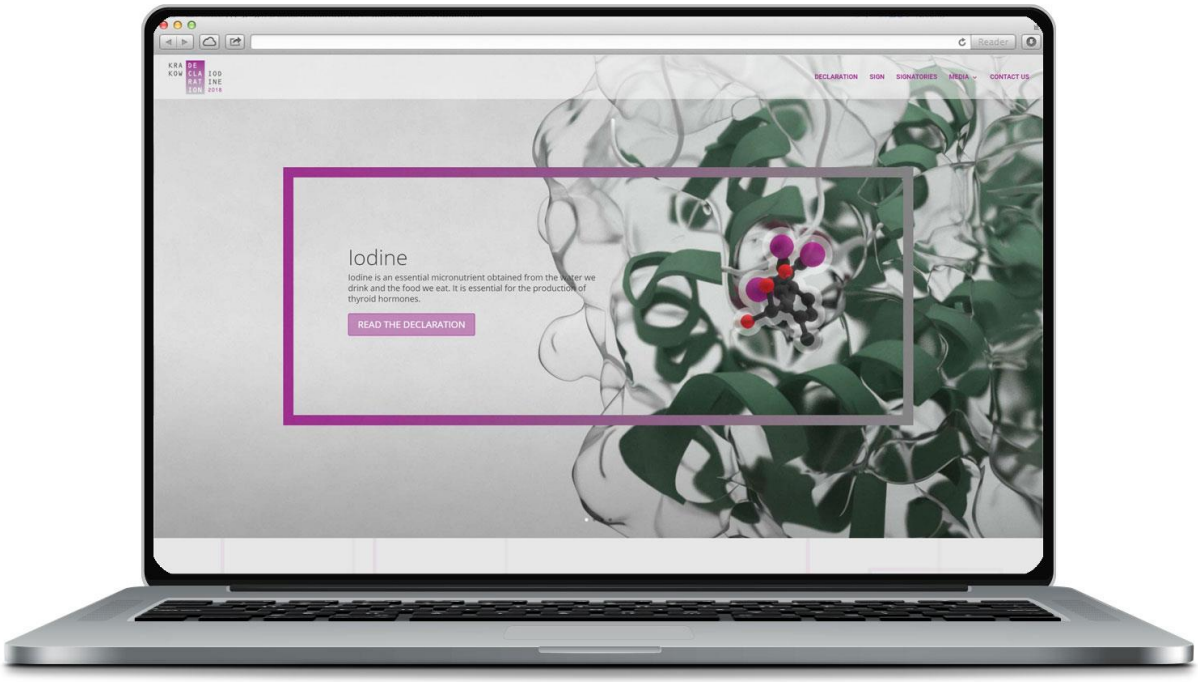

Figure 8: Krakow Declaration on Iodine website (www.iodinedeclaration.eu) ©biolution GmbH

Regional monitors formed a crucial element in the coordinated strategy and were highly active both in introducing the EUthyroid project and its aims to relevant policy makers and disseminating the project outcomes (such as the Krakow Declaration on Iodine). Addressing the 27 countries that make up EUthyroid with their different backgrounds and requirements necessitated an adaptive approach to ensure all partners received the level of support they required to achieve change. Face-to-face meetings with policy makers occurred in 20 countries, with several of these already yielding policy change.

One of the main dissemination objectives was to publish a white paper (position paper) and this was successfully achieved with the simultaneous acceptance by the European Thyroid Journal of both the EUthyroid white paper and the Krakow Declaration on Iodine in April 2018. This was published on 10th July 2018 and is expected to considerably aid the activities of regional monitors in their efforts to motivate policy makers.

3. Progress beyond the state of the art and potential impacts (including the socio-economic impact and the wider societal implications of the project)

EUthyroid aimed to progress beyond the current state of the art, characterised by fragmented national strategies towards iodine deficiency prevention, through the harmonisation of: existing registry and monitoring data; guidelines for study conduction; training of study staff and measurement of samples. The project focused on working towards voluntarily harmonised national activities to provide its impact.

The consortium devised a set of measures to initiate harmonised monitoring based on existing national initiatives, to conduct research on IDD outcomes that provide crucial evidence to support the effectiveness of IDD prevention programmes and start building the capacity for harmonised action to tackle IDDs. These research activities were underpinned by a meaningful dissemination programme engaging stakeholders at a local and regional level to promote the harmonisation of existing monitoring and prevention programmes. This will support improved health outcomes in the long term, ensuring a healthier diet and a better quality of life for European citizens. On a policy level, this will reduce health inequity in Europe and the burden of IDD on European health care systems.

Developing new methods

Currently iodine status in populations is assessed through measuring urinary iodine concentration (UIC) in sufficiently large samples. As UIC varies with daily intake, multiple measurements would be necessary to assess the iodine status in individuals, an unfavourable approach for IDD monitoring. EUthyroid was the first project to evaluate DBS thyroglobulin as a promising functional biomarker for individual iodine status.

Measurement of DBS thyroglobulin is an innovative, inexpensive, paper-based method of iodine status assessment at the population and the individual level. This promising method was developed, further optimised and evaluated in diverse country cohorts. During the course of the project its usefulness in high-risk groups (e.g. pregnant women and women of reproductive age), as a potential individual iodine status marker and as a component of IDD monitoring in different health-care systems was tested.

Evaluating the effectiveness of IDD prevention programmes

Given the low cost of fortification of table salt within IDD prevention programmes and the moderate efforts necessary to conduct meaningful monitoring across Europe the cost effectiveness of programmes to eradicate IDD appears a reasonable presumption. However, no health-economic research has been reported for Europe and EUthyroid is

the first project to investigate the cost-effectiveness of IDD prevention programmes in regions with mild-to-moderate iodine deficiency. These data will provide a sound basis for policy makers to assess current IDD prevention and monitoring programmes.

Moreover, the first decision-analytic model answered questions about the cost-effectiveness, long-term effectiveness and benefit-harm balance of iodine fortification in the general population of a European country with mild to moderate iodine deficiency. EUthyroid provides information about the benefits (e.g. the reduction of iodine deficiency diseases), risks (e.g. the increase of iodine induced diseases) and costs of prevention and monitoring programmes for IDD in Europe to guide clinical and health-policy decision making. The model was used to analyse, whether prevention and monitoring programmes for iodine deficiency diseases are - in the long run - more beneficial than harmful and whether these programmes are worth their cost. With this work, the first summary and systematic synthesis of relevant evidence in the field of prevention of IDD was provided. It is anticipated that the model will be updated in the following years and adapted to different European countries to provide country-specific guidance in health decision making. The relevant barriers and challenges for the implementation of IDD prevention and monitoring programmes in European countries surveyed by EUthyroid should be used as a starting point in the implementation process of prevention measures and for a regular standardised monitoring.

Mapping iodine status

Europe is highly diverse in respect to iodine status, which ranges from moderate or mild deficiency to sufficiency. IDD prevention programmes are therefore not of universal concern across Europe, with many countries lacking commitment to monitoring and prevention programmes and their harmonisation. The highly diverse status results in a considerable lack of momentum for a pan-European approach in IDD prevention, which EUthyroid strived to overcome.

The EUthyroid consortium was able to improve the standardisation of population-based iodine and thyroid studies. As one of the main outcomes, maps of iodine status and the prevalence of thyroid disorders and disease in Europe were generated. Of particular note, inter-laboratory comparisons revealed major deviations compared to standardised results, which clearly demonstrates the importance of continued standardisation and harmonisation in the field.

From a methodological point of view, the experiences from EUthyroid are valuable. The project set out to apply different types of methodologies, depending on the research question, rather than choosing one approach. Combining registry data with laboratory data, obtained by tailored laboratory methods validated for research purposes, yielded a

leap in knowledge, i.e. the most comprehensive view of the iodine and thyroid status of European populations so far.

Uncovering health inequalities

Iodine status is well known to vary significantly resulting in inequalities in IDD throughout the population. EUthyroid sought to uncover these health inequalities and analyse them in relation to socioeconomic factors in various European countries with different IDD prevention programmes. Particularly, access to adequate iodine supply in countries with voluntary iodine fortification may give rise to social disparities in IDD prevention. However, other socioeconomic parameters may exist determining health inequalities, as some gourmet salts are not fortified and in particular health-conscious people frequently reduce their salt intake to lower the risk of cardiovascular diseases. The extensive data assembled within EUthyroid forms a sound basis to investigate health inequalities in Europe with respect to IDD and are expected to lend further support for a harmonised, pan-European approach to IDD prevention.

In the EUthyroid database, data from nine European countries (Bulgaria, Croatia, Cyprus, Germany, Finland, Latvia, Macedonia, Spain, Turkey) comprising a total of over 20,000 children and 29,000 adults were analysed to study the association between indicators of socioeconomic status, iodine status and thyroid related biomarkers. Studies from Germany, Latvia, Macedonia and Spain in children showed that higher parental education or higher overall family affluence was associated with higher intake of iodised salt in children. Contrary, in adult populations higher educated groups showed a tendency towards lower urinary iodine excretion in Germany and Finland. Urban residence was associated with higher iodine excretion and higher intake of iodised salt in Spain, whereas urban residence was associated with increased thyroid hormone (indicating a thyroid dysfunction) levels in Bulgaria. Overall, the results suggest that socioeconomic imbalances likely influence the iodine supply and thyroid-related disorders, but the pattern varies between different regions. This may possibly be due to disparities in IDD prevention measures (voluntary vs. mandatory) and their contribution to persistent health inequalities can be further assessed through decision-analytical modelling established within EUthyroid.

Understanding the effect of iodine deficiency on offspring neurocognition

The major societal concern associated with iodine deficiency is the negative impact on neurocognition in the foetus and children. Given empirical evidence for a correlation between mean national IQ and the gap between rich and poor countries, it is of important societal concern to provide sufficient iodine to the next generation and, moreover, if

inequalities of iodine supply exist, to ensure the chances of societal advance for those at economic disadvantage.

For the European ambition to maintain an innovative economy over the forthcoming decades, an intelligent and educated workforce will be essential. Therefore, IDD prevention should be a priority in Europe.

The effects of maternal mild-to-moderate iodine deficiency on children cognition were relatively unexplored. EUthyroid overcame this knowledge gap by providing new data on maternal iodine status in relation to neurodevelopment. This encompasses an important gender aspect in IDD prevention as women of childbearing age are a major group at risk owing to increased need for iodine during pregnancy. EUthyroid addressed this challenge by providing new insights into the association between iodine status of pregnant women and neurocognitive function in their children and by providing infrastructure to standardise regional studies in women of childbearing age and pregnant women. Further advocacy on thorough subclinical thyroid disorder screening of pregnant women and women of childbearing age should incorporate EUthyroid standardised methods for evaluation based on these findings.

Leading policy change through dissemination

Despite the known health risks associated with IDD and the consequent burden on European health systems, IDD has not been on the political agenda in most European countries for more than a decade. Due to its assigned low priority, the importance of IDD for individual and public health remains low even among public health researchers. Consequently, there is only minimal public concern about IDD-related health consequences with very limited knowledge about national iodine deficiency monitoring and prevention programmes.

EUthyroid has sought to address all of these stakeholder groups through targeted dissemination activities. Policy makers were addressed specifically through the Krakow Declaration on Iodine, which created significant resonance as evidenced by the number of organisations, both national and international, who provided expressions of support for the declaration. EUthyroid regional monitors enabled EUthyroid to address the particular national situations across Europe through targeted dissemination to policy makers. Meetings to disseminate EUthyroid outcomes are ongoing but have already resulted in action towards policy change in a number of countries, notably in Greece, Denmark, Spain and Hungary.

The scientific and public health research community was addressed by the EUthyroid white paper and various publications, of which more are in preparation, significantly that

of the first decision-analytic model to explore the long-term benefits, risks, costs, and cost effectiveness of prevention of iodine fortification.

Across Europe the general public have been informed about the problem of IDD and the EUthyroid project through social media campaigns, press releases and the work of EUthyroid partners to obtain exposure through the press and TV and radio interviews reaching large audiences.

It is hoped that the dissemination of EUthyroid outcomes has put the important issue of IDD back on the political agenda at least on the national level across Europe.

Conclusions

EUthyroid conducted the most in-depth analysis of iodine deficiency and health outcomes and provides a solid foundation of data to fill the current lack of health outcome research, a major stumbling block to initiating national monitoring and prevention programmes. The expectation is that EUthyroid infrastructure and policy recommendations with continue to pave the way towards Europe becoming the benchmark for IDD prevention worldwide.