DoReMi - Low Dose Research towards Multidisciplinary Integration

Report on DoReMi TRA and position paper: Consensus meeting for position papers on consequences on risk assessment and radiation protection

29-30 April 2015

Sitges, Spain

Organisers: Dietrich Averbeck (IRSN/CEA, WP2 leader) and Sarah Baatout (SCK-CEN, GA chair)

Contents

1. Objectives of the meeting

The DoReMi Consensus meeting for position papers on consequences on risk assessment and radiation protection was related to WP2 Task 2.3.7 and the Milestone 2.5 (due by month 66, i.e. June 2015).

Following several WP2 TRA founding meetings held previously (for example, Saint Feliu de Guixols, Barcelona, Spain May 2010; Vietri sul Mare, Italy, Oct 2012) to specify the DoReMi NoE methodology including (1) definition of uncertainties in the assessment of health risks from low doses and in radioprotection (2) definition of key questions (as well as related subquestions) to be answered ((3) definition of main research needs, and (4) the research strategies for low dose health risk research to be implemented within DoReMi (6 years) (see Transitional Research Agenda, TRA) and MELODI (>20 years)(see the Strategic Research Agenda, SRA). Since DoReMi ends the 31st of December this year (2015) it is timely to collect and summarize specific and general outcomes of the project.

The DoReMi consensus meeting aimed at getting an overview of the work accomplished so far (mid-April 2015) in the Work packages WP3-7 (WP3: education and training, WP4: infrastructures, WP5: shape of dose response, WP6: individual sensitivity and WP7: non cancer effects) on the basis of published DoReMi papers and foreseen papers, main messages and outcomes, answers provided to the DoReMi key questions (and subquestions), and identify remaining research needs and priorities for future research.

The meeting was expected to help structuring and defining the expected contents of the position and policy papers. The position papers should summarize the main outcomes of the DoReMi WPs work (education and training, infrastructures, cancer, individual sensitivity and non cancer), and the policy papers should formulate main messages derived from this work for better low dose health risk assessments and a general improvement in radiation protection.

Thus, this workshop was to focus (1) on getting an overview on DoReMi results, and (2 through selected contributions, highlighting of current studies in epidemiology, biomarkers and biodosimetry, immunology, cancer risk assessment, modeling and systems biology in the European and international context. Together with a contribution from EAB this should facilitate the management of DoReMi papers (including forthcoming ones) (WP2 task 2.3) and the preparation of the DoReMi position and general policy papers (WP1-7).

1.1. Issues of discussion

- Position papers: what for?
- Policy paper: what for?
- Assessment of actual DoReMi papers: with (and without?) acknowledgment of DoReMi, directly related to main DoReMi issues
- Outcomes of DoReMi papers in relation to the European and international context of research activities
- Future research needs and strategies to be underlined for MELODI, OPERRA, CONCERT, etc.

1.2. Programme Committee

The programme committee was established and proposed at the last DoReMi GA in Munich in July 2014:

- Elisabeth Cardis, CREAL
- Ulrike Kulka, BfS
- Sarah Baatout, SCK•CEN
- Sisko Salomaa, STUK
- Peter Jacob, HMGU

The programme committee was in charge of organizing and initializing the preparation for the Consensus meeting. This meeting related to the preparation of position papers was for DoReMi consortium members (RTD activity, summarizing DoReMi results and discussing the DoReMi policy and position papers.

1.3. List of attendees (14)

- Sisko Salomaa (STUK, FI): sisko.salomaa@stuk.fi
- Dietrich Averbeck (IRSN/CEA, FR): dietrich.averbeck@irsn.fr
- Sarah Baatout (SCK-CEN, BE): sbaatout@SCKCEN.BE
- Elisabeth (Liz) Ainsbury (PHE, UK): elisabeth.ainsbury@phe.gov.uk
- Jean-René Jourdain (IRSN, FR) (April 30 only): jean-rene.jourdain@irsn.fr
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- Markus Eidemüller (HMGU, DU): eidemueller@helmholtz-muenchen.de
- Richard Wakeford (EAB member, UK): richard.wakeford@gmail.com

1.4. DoReMi TRA: 9 main key questions concerning cancer and non-cancer effects: Epidemiological and mechanistic studies

1. What is the dependence on energy deposition?
2. What is the dependence on dose rate?
3. What are the tissue sensitivities?
4. What is the modification of risk by genetic and epigenetic factors and gender?
5. What is the effect of age on risk?
6. What is the effect of lifestyle and/or other exposures on risk?
7. What is the effect of physiological state?
8. Is there a hereditary component in risk?
9. What is the role of non-targeted effects in health risk?

2. Programme and discussions of the meeting

The original programme was adapted as much as possible to the actual availability of the speakers, because some of them were also participating in the parallel DoReMi workshop of Epidemiologists and biologists organized by Elisabeth Cardis (CREAL) at the same location (Port Sitges Resort Hotel, Sitges, Barcelona, Spain, 29th and 30th April 2015). Thus, the actual final programme proceeded as follows:

Wednesday April 29th, 2015

Main thematic of the day: link between the 9 key questions of the DoReMi TRA and the work of the DoReMi WPs.

Morning session

8:30-9:00 Welcome of the participants

9:00-9:10 Sisko Salomaa (STUK, FI), Sarah Baatout (SCKCEN,BE):
Objectives of the meeting; Progress in DoReMi TRA settings

Elisabeth Cardis (CREAL, CAT): Objectives of the current meeting: Review of state of the Art and lessons learned in DoReMi

9:10-9:20 Dietrich Averbeck (IRSN/CEA, FR): Introductory remarks

Dietrich introduced the participants, program committee, purpose and aims of the meeting and gave a short overview on the expected amendments of the program during the meeting.

9:30-10:10 Dietrich Averbeck (CEA/IRSN, FR): Summary of the methodology defined for the TRA setting, key and sub- questions-Structuring the key questions and sub-questions of the TRA to the related tasks and outline of future TRA

Dietrich reported on the DoReMi TRA concept, the DoReMi key questions and sub-questions (the latter should still be checked by the WP leaders and WP task leaders) and the recalled the steps in TRA development, gave a preliminary table on the contributions of the WP tasks to the 9 key questions in terms of publications (April 2015), the TRA methodology adopted so far (state of the art, list of questions and sub-questions, priority setting, broad consultation, suggestion for new research projects, activities and preparation of calls and of a Roadmap) . Also, he proposed a structure and some contents for the final DoReMi TRA to be set up before the end of 2015.

10:10-10:45: Discussion

Peter Jacob: suggested:
(1) According to recent MELODI SRA Working Group discussions, the preparation of EU calls was up to now not optimum. The selection of topics out of a list of priorities was not necessarily supporting the development of new ideas. Thus, a different way is proposed (going back to the old FP system): set as general task health risk assessment in radiation protection and see who can propose the best contribution to that. Do not take out of the list of TRA research priorities a few selected ones for the next call but prepare a broader call integrating most of them (around risk assessment).

Dietrich: This will constitute a change in strategy. Up to now it was thought that all topics of the TRA priorities were important (although some could have been more specific (Sisko), and so, each call gave the possibility to realize a few of them, the others were left over for the next, forthcoming calls. This had the advantage that finally all priority subjects were considered according to their timeliness and urgency. Vere: Unfortunately, not much money was available for each call. Thus, main streams of research should continued to be supported and a balance been sought between calls corresponding to specific questions and more general calls. Peter: The next call should focus on low dose risk. Ulrike: Several low dose research platforms should be involved.

(2) Peter pleaded against establishing Roadmaps. *They always will be preliminary, better concentrate on key questions, for example, in what dose range one can approach the DoReMi key questions? What is the current feasibility for that?* Sisko replied: Roadmap illustrates the way to the long term vision: how to reach it, what you need to do first to get to the next level. Roadmaps are useful for getting a time scale for what is achievable and feasible, and afterwards, what has been achieved and what has not? Roadmaps facilitate to judge what has been achieved in the time allotted. Dietrich: to the list of proposed items one might add: Modeling of IR-induction of pathologies, the Systems biology approach and Analysis by Bioinformatics.

(3) Peter: Can health risks of cancer and non-cancers be compared? Here, dose comparisons are important. It seems that there is now more evidence than expected for CDV and cancer risk induction for doses around 100 mSv. Can non-linearity be revealed? What is the effect of moderate and protracted exposures? Where should the research money go?
Richard: I am somewhat sceptical about the current epidemiological evidence for CDV induction at low doses. It is important to properly understand this issue because CVD risks could be incorporated into dose limits? A critical view can be taken of the cohorts currently providing "positive" results: BNFL workers, Mayak workers (although only really from incidence data, and not mortality data, and the impact of migrant worker data needs to be fully assessed), and the Chernobyl liquidator incidence data.

11:15- 12:15 Liz Ainsbury (PHE, UK) (on behalf of Simon Bouffler): Results obtained within DoReMi WP5

WP5 Outcomes: There has been substantial progress in exploring dose responses (evidence for non-linearity) but the big challenge remains to relate those to lifelong responses. In April 2015 we counted about 40 publications with a peak for Task 5.2. Increases in publications are: on dose and dose rate effects, carcinogenesis, immune functions and biophysical interactions (models).

12:15-12:40 Discussion: (as well as during presentation)

Future: research community consensus and a clear direction are needed. For the position paper of WP5, it would be helpful to mention actual mechanistic cancer induction models proposed (mutational model, stem cell related model…) and report the implications from WP5 results. It would be nice to put emphasis on how DNA responses relate to cancer risk (linear DNA response/ non linearity after repair?, on promising biomarkers (including telomeres (Ulrike)) which should be validated. Non-linear radiation responses are demonstrated in the low dose and moderate dose range. The CURE project (Uranium Occupational exposure) based on the cooperation of epidemiologists, dosimetrists and biologists is very promising (due to the use of biomarkers), had a successful start and looks feasible.

Afternoon session

14:00-14:30 Peter Jacob (HGMU, DE): Modeling of cancer risk (experience from EpiRadBio)

Peter gave a detailed overview on recent knowledge obtained on colorectal cancer and thyroid cancer development, models and the implication of biomarkers (MSI , APC and MLH in colon cancer) and CLIP2 involvement in Thyroid cancers from the UkrAm cohort.

14:30- 14:50 Discussion

Conclusion put forward for the TRA:
Biomarkers for IR induced cancers are useful for detecting individual sensitivity and assigning the probability of causation (attributability). However, the biomarker concept could not be shown to improve risk estimates.

This shows that there is a need for:

- Biomarkers for different types of cancers
- System biology to derive disturbed cellular networks
- Cellular or animal models to determine function of disturbed network
- Measurements of the frequency of biomarkers in radio-epidemiological cohorts
- Models of processes leading to different types of cancer
- Optimization of the models by adaptation to radio-epidemiogical data.
- Consistency checks of the models with biomarker data
- Risk estimation based on biologically validated models

Good example for this: recent publications by Abend M. et al. 2014 Radiat Res Sept 182(3)299-309, and Abend M. et al. Radiat Res. 2015 Mar 183(3)249-261, systems biology approach, relating biomarkers to cellular networks, biological models for functional disturbance.

14:50-15:20 Markus Eidemüller (HGMU, DE): Modeling and systems biology

Markus presented a very informative overview on the modeling of the risk of lung cancer by radon exposure (ELDORADO cohort), the lifetime risk of breast cancer (Swedish Hemangioma cohort) from Radon and /or X-ray exposure and the risk of lung cancers in the Mayak cohort from plutonium exposures. The studies on epidemiological cohorts carefully investigated the risk dependence of factors like age, lifestyle or other factors, e.g. familial risk, if the data were available. In the publication concerning the Eldorado cohort after radon (WP5.4) mainly effects of dose, dose rate and age were investigated.

15:20-15:40 Discussion

Comments: Risk uncertainties at low doses are important, how individual risk factors can influence population risk? There is need for knowing more on underlying mechanisms, links should be sought between identification and quantification of pathways and mechanisms and systems biology and epidemiology studies. What are the gene mutations driving carcinogenesis and what are the connected pathways involved? How does radiation contribute to disturbance of these driver genes and pathways?

Dietrich: What about the French cohort on hemangioma? Markus: this cohort appears to be as yet too small for actual health risk evaluation. Richard: In all these studies one notes the absence of work on leukemia. Sisko: When is radiation acting as carcinogen? Is it acting as an

initiating mutagen or acting later as a promoting agent? Can one do something against cancer development even after radiation exposure?

Sisko: Future workshops are proposed on (1) lifestyle effects and (2) age effects on cancer and/or non-cancer development.

16:20-17:20 Laure Sabatier (CEA, FR): Relation between key questions and infrastructures

Laure gave very detailed overview on the outcome of the different tasks of WP4 and the Infrastructure- CONCERT meeting held 27-28 April 2015 in Sitges. She presented a complete and very valuable account concerning (1) irradiation facilities (2) Data-and biobanks (3) cohorts (4) analysis platforms, their establishment and present and future use in Europe in view of establishing a general roadmap on infrastructures for OPERRA and CONCERT.

17:20-17.30 Discussion

Comments: Relationship to E&T: Infrastructure information should be included in E&T in order to harmonize procedures and facilitate integrative mobility.

Infrastructure issues are also important for setting up future calls.

Implications for position paper: Infrastructures are useful for scientific community (excellent IR facilities, data and bio-banking and storage facilities (see STORE), signaling of suitable cohorts (for molecular epidemiology) and analysis platforms with standardized procedures (ISO).

17:30- 18:00 Ulrike Kulka (BfS, DE): Biomarkers and biodosimetry

Ulrike presented critical overview useful biomarkers for radiation exposures and pathological effects) with a lot of emphasis put on quality assurance, quality management (standardization) and E&T (based on the experience of RENEB.

18:00-18:20 Discussion

Comments: There is need for new biomarkers that can be used for in vitro and in vivo studies. The new and upcoming biomarkers have to be critically and carefully validated with regard to their field of application (for example using biobank samples and archived material). For better comparability of the results between the laboratories the methodic protocols have to be standardized and harmonized as best as possible. In addition, knowledge on the correct use of biomarkers has to be transmitted (E & T). Their use in emergency cases should be studied as well with regard to the special requirements in such situations. Regarding well established biomarkers, the consistent high quality of application has to be ensured by adequate quality assurance measurements.

Proposal for the future: biomarkers issues should be included in Infrastructures as well as in in E & T with special focus on QA & QM for new biomarkers and for well established biomarkers. All future projects should include a part referring to infrastructures.

Thursday April 30th 2015

The second day included presentations on the outcomes of WP7 non cancer effects , the importance of Immunological aspects, the way forward in Epidemiological research, the importance of integrating non cancer and neurological aspects, the importance and achievement

of WP3 E&T in DoReMi as well as a brief DoReMi paper overview on results obtained in WP6, Successful items in relation to DoReMi publications, a critical comment from EAB, and a summarizing overview on DoReMi messages that may facilitate establishing the DoReMi statement, updating the DoReMi TRA and structuring the position and policy papers.

Morning session

8:30-9:00 Welcome to new participants

9:00- 10:00 Jean-René Jourdain (IRSN, FR) Non cancer effects: WP7 activities & publications with reference to DoReMi

Jean-René presented a critical overview on DoReMi WP7 peer-reviewed papers published with reference to DoReMi and concerning different tasks of WP7. A total of 25 publications were analyzed according to different parameters (timing, tasks and partners) involved. The analysis concerned the first 6 tasks of WP7, 6 other tasks plus the subtask are still ongoing.

Comments: Among the 25 publications already available only 9 publications brought some answers to the DoReMi key questions. Key results were obtained on the ELDO project, the involvement of DNA damage, the modulation of inflammatory responses and on vascular effects. Three main publications on vascular effects show non-linear low dose-rate effects, induction of senescence and mechanisms involved.

10:00-10:20 Discussion

Comments: It was noted that not much information is yet available on higher dose rate effects on non- cancer effects.
→ Because some DoReMi partners published task-related facts without especially referring to DoReMi, it was thus agreed that the results of those papers should be allowed to be mentioned in the final position paper(s) of the WP. Some review papers referring to DoReMi (not necessarily presenting new results) may be mentioned as well.

Vere, Serge: Immunological effects were recognized to play an important role in IR effects. Thus, immunology should be considered as an additional cross-cutting issue in low dose radiation research.

Sisko called for some caution using the metrical analysis of DoReMi publications because of possible false negatives (no DoReMi acknowledgement but actually DoReMi results) and false positives (acknowledging DoReMi but indirectly related) coming up. Not many publications were actually on low dose (<100 Gy).

Vere: in DoReMi position papers we should stick to science according to the TRA, and in the DoReMi policy paper we should give the paradigm developments that are important for radiation protection.

Sarah: In the discussion on non-cancer effects, results of the ProCardio project should be considered as well. Concerning neurological effects, it is felt that some issues resulting from the CEREBRAD project should be also considered together with the DoReMi outcomes, in particular when they indicate what could be done in the future.

Jean-René: Because there is no money left in DoReMi, the organization of a specific DoReMi WS on neurological effects of IR has been skipped.

10:20-11h20: Serge Candeias (CEA, FR): Immune system and low dose radiation: Why, What and How?

Serge gave a detailed overview on the different ways IR can activate the immune system and modulate immune responses and presented important results from several important research lines initiated within DoReMi (see ModInIR, CyRAID, MIRACLE,..) and the main conclusions of the exploratory DoReMi Workshop held November 2013 in Budapest, The results suggest that the immune status can affect the individual IR response. Relatively low doses of IR (in the range of 0.5 Gy and above) can modulate inflammation and anti-inflammatory responses; non-linear responses are observed that may have an important bearing on the development of cancer and non-cancer diseases. Of importance are the genetic and epigenetic control of the immune system and its relationship to the defense systems such as DNA repair and antioxidants.

Results of the discussion: Important issues to be tackled are: possible thresholds in IR for the activation of the immune system and the modulation of immune responses, the effect on individual radiation sensitivity, antitumor effects of IR and the relationship between immunological responses and bystander (and abscopal) effects following low dose exposures.

11h45-12h45: Andrea Ottolenghi (UNIPV, IT), speaker: Vere Smyth (UNIPV, IT) Relation between key questions and E & T

Vere gave a very informative overview on the achievements made within DoReMi WP3 concerning WP3: he focused on the themes of present (11) and forthcoming courses in relation to the DoReMi key questions and the striking development of integrated E & T courses (also through the annual ET Forum (as annex of the yearly MELODI WS), future aspects of sustainability through the new MELODI E&T Working Group and through OPERRA and in CONCERT (with 5 platforms).

12:45-13:00 Discussion

Comments: Important discussion points were: how to get feedback from successful courses in order to better promote new ones? Relationship between DoReMi E&T activities and the follow-up by MELODI; next generation E&T, dissemination of courses to the research community (up to now also with WP2 and the website), how to develop further awareness and use of infrastructures (in line with WP4); development of specific courses targeted to specific platforms, how to introduce and cover new areas of expertise, technologies and disciplines (omics, bioinformatics).

New ideas: search for new topics, new types of courses, look for new top down organization of courses rather than for new calls and partners for proposals, initiate special training grants to participate in courses (within CONCERT?), include a Training session and posters in next MELODI WS, look for further integration at the European level (networking). Andrea: seek to contribute to existing courses (courses for medical doctors and others, in CONCERT?) and export low dose research concept and keep the high quality of the courses, establish a flying group of 'teachers'. Keep present expertise alive in E&T courses.
Proposal: All new proposals should include an E&T part and follow on the E&T strategy, also after OPERRA including RTD dissemination.

Afternoon session

14h30- 15:00: Epidemiology: the way forward, Elisabeth Cardis (CREAL, CAT)

Elisabeth gave an overview on the outcomes of the meeting of the DoReMi cross-sectional task group in epidemiology (E. Cardis, J. Hall, M. Kreuzer, D. Laurier) and the DoReMi-think-tank of epidemiologists and biologists (see Pernot et al. 2013 and present meeting May 2015) and the WP7 molecular epidemiology strategy for research on CVD . The presentation focused on suitability of biomarkers of exposure, susceptibility, late and persistent effects, epidemiological study design, suitable epidemiological cohorts (radiotherapy patients, medical diagnosis, workers, transgenerational effects (genomic instability, epigenetic markers), genetically predisposed individuals).

Recommendations:
For exposures above 100 mGy, dicentrics and changes in RNA expression signatures (low and high doses may differ!), for individual susceptibility, GWAS, and for diseases CLIP2 and 7q11 (thyroid cancer) and pre-leukaemia markers (still to be validated) are found to be useful. (Several markers from omics and epigenetic studies are thought to be forthcoming as well). Suitable cohorts for studies (of low and high doses) on cancer and non-cancers (that may include biological sampling and suitable biomarkers) are thought to consist of RT patients, CT patients, nested control study, transgenerational and mutigenerational studies (Techa River, Oserzk), workers (Nuclear: Mayak (SOLO), Sellafield, and current workers elsewhere; miners (Wismut)), South African Gold miners, and new cohorts (mines of Mozambique) and Liquidators (Chernobyl) and interventional cardiologists. Studies to validate CLIP2 and 7q11 in cohorts of thyroid cancers (INT-THyr) as a second cancer following RT in childhood and pre-leukaemic condition feasibility study on birth cohorts are useful as well.

Comments: Richard: for transgenerational studies, the work on minisatellite mutations has only shown positive results from one group and has not been conformed by others. The latest "negative" paper, on Sellafield workers, has just been published.

Proposal: Building up an exposure cohort study RADMAD 'RADiobiologist longitudinal MultiAssay Discovery' (consisting of volunteers over 55 with whole body CT and biological sample collection and long term follow up).

15:15- 15:30 Dietrich Averbeck (IRSN/CEA,FR) (in the absence of WP6 leader Mike Atkinson): WP6 outcomes according to DoReMi publications

Following the DoReMi Barometer (see website) and the assessment of available DoReMi publications (April 2015), Dietrich reported on 12 publications attributed to WP6: Task 6.1: Flockerzi E. et al. 2014; Task 6.2: Gürtler A et al. 2014, Pottier G et al. 2013, Rosemann M et al. 2014, Shim G et al. 2014; Task 6.4: Perriaud I. et al. 2014, Sagne C et al. 2013 and 2014.

Dietrich gave a preliminary account on the scientific outcomes of WP6. For example, Task 6.1: DNA repair and repair capacity in the lung in different mouse strains: differences in 53BP1 induction in bronchiolar and alveolar epithelial cells. Fractionated doses (100 mGy daily) increase toxicity and probability to induce secondary malignancies.

Task 6.2: 10 Gy of gamma rays induced individual differences in proteomic profiles are low compared with inter-individual differences seen in lymphoblastoids cell lines.

Task 6.2 (and task 5.1 ?) Lead exposure induces telomere instability in human cells by perturbing telomere replication on the lagging strand. This is important in brain development and neurotoxicity. Alpha-ray induced osteosarcoma and different tumor susceptibility genes in

mouse strains: Reduced Rb1 expression by common variants in regulatory regions can modify the risk for malignant transformation of bone cells after IR exposure.

Task 6.2 Review: Cross-talk between telomere maintenance and radiation effects. Telomeres are key players in the process of IR-induced carcinogenesis.

Task 6.4: Intronic TP53 polymorphisms affect G4 formation and expression of isoform specific transcripts of the TP53 gene.

-Meta-analysis of cancer risk associated with a specific rS17878362 polymorphism of the TP53 tumor suppressor gene. The cancer is increased for homozygous A2A2 carriers for breast and colorectal but not for lung cancer. rs17878362 is associated with increased cancer risk with a population and tumor specific effects.

-Age effect on cancer onset in Li-Fraumeni/Li-Fraumeni-like syndrome. Dependency on G4 polymorphisms in haplotypes of the WT TP53 allele.

Task 6.6: Pernot E. et al. 2012, Pernot E. et al. 2014; Task: 6.8: Maguire A et al. 2015 a and b.

Messages from WP6**:** Changes in energy metabolism (mitochondrial functions) may play an important role in individual R responses. Proteomic profile analysis reveals individual differences after 10 Gy: changes involve alterations in energy metabolism and mitochondrial functions. In mice, fractionated IR may lead to a higher probability of cancer. An epidemiological study shows a dose-rate effect on lung cancer risk in uranium miners. Gene polymorphisms play an important role in breast and colorectal cancer susceptibilities. Raman spectroscopy profiles can reveal individual IR responses. Telomere functions are involved in individual responses

15:30 Sisko Salomaa (STUK, FI): Successful items in relation to DoReMi publications and way forward and General Discussion on proposal for TRA position paper and DoReMi policy paper.

It is proposed to highlight the DoReMi work at the end of the DoReMi project. There is consensus that relevant outcomes from each WP should be written up by each WP leaders in separate papers. These will then be proposed for publication as a special issue as a series of papers in Progress in Biophysics and Molecular Biology (first option*). Following a suggestion made by Simon Bouffler after the Sitges meeting, the main purpose of the position paper should be clearly defined, possibly also a common format (<20pages ?, research areas (2-3?)) for each WP correspondingly with willing authors together with the draft of a general editorial.*

The overviews presented in this WS have been very useful but may be still somewhat confusing for people outside DoReMi (Sarah Baatout). Thus, some more work is required by WP leaders and WP task leaders to define who is going to synthetize the work, and where to put future efforts (Sarah).

It is also agreed that (1) a DoReMi TRA statement should be prepared (first draft by Dietrich) before the end of June (useful for MELODI and CONCERT) in order to substantiate the present view of DoReMi on low dose risk research: present status, where to go and what to do next (linking molecular mechanism, epidemiology and modeling links with health risk assessment). The updated TRA should then give the more radiobiological insights gained within DoReMi together with a future vision and proposed Roadmap in a stand-alone document.

Sisko: After discussion on DoReMi position paper and policy paper the following decisions have been taken:
Following the WS a short TRA statement will be drafted that should present our point of view (where to go, how to link mechanisms, epidemiology and modeling to risk assessment) and should be useful for MELODI and CONCERT, the TRA will be updated (stand alone document with radiobiological information and DoReMi vision together with a possible schedule (Roadmap) for future research activities),
The main results of the DoReMi WPs will be highlighted in a series of position papers written by the WP leaders.

Possible Journal (following a suggestion by Simon Bouffler): Progress in Biology and Molecular Biology (DoReMi dedicated special issue), but also other journals may be considered (Mutation Research Reviews etc.)

16:00-16:30 Dietrich Averbeck (IRSN/CEA,FR): Messages from DoReMi papers: outline for position and policy papers

16:30-17:00 Richard Wakeford (EAB member, UK): Useful comments and propositions

Richard addressed a few points that are helpful to appreciate how successful the work of DoReMi has been:

Have the following main issues successfully been treated within DoReMi?

- Low dose (acute dose <100 mGy low LET radiation) or low dose-rate (<0.1 mGy/min averaged over an hour) (>10,000 nuclear workers in UK accumulated doses in excess of 100 mSv over many years, and this could tell us a lot about protracted exposure)
- Apply DDREF of 2: Still controversial. (Lifespan studies from A-bomb survivors suggest a factor of <2)
- Appropriateness of assumption of linear-quadratic dose-response (valid for some cancers, not for others)?
- Appropriateness of boundaries of 100 mGy and 0.1 mGy/min?
- Is the dose-response the same for all cancers? Unlikely (e.g. leukaemia and solid cancers).
- Why the difference for different cancers? Important for understanding of radiation-induced risk.
- How is the radiation-induced risk influenced by the background risk? Implications for individual radiosensitivity (influence of age and lifestyle on radiation-induced risk) and transferring risks between different populations.
- Is there a CVD risk at low dose/dose-rate? Is there a threshold or not?

Proposal: The TRA should also consider these questions and to what extent they have been addressed.

Discussion: How much does DoReMi address the DDREF in risk estimations?

The definition of low dose and low dose rates is crucial to discuss dose responses for different cancers. Why leukaemia is somewhat special? Deviations from linearity are fundamental. The inherent components of individual radiation sensitivity have to be determined separately from the other components (lifestyle, other exposures…). A solid scientific basis for DDREF should be sought.

Andrea: The HLEG concepts still hold. Vere: Is the research money well spent when the risk of low doses is low, and does not more research get more understanding but also complicating the

issue. Markus: Focus should be put on low dose risk models on what are the effects which are important for cancer induction What are the issues to push knowing that many metabolic pathways are involved? Sisko: The DoReMi TRA statement should include the state of the art also on genetically defined individual susceptibility. Serge: Immunological aspects should be included even if adding another dimension of complexity. Andrea: Systems biology should be pushed. Laure: Infrastructure networking in Europe should be pushed as well. All new projects should include a part on E&T.

Dietrich (final remarks): The participants are particularly grateful to the organizers in particular to Elisabeth Cardis and Bill Hempel who did such a great job in choosing the very convenient Port Sitges Hotel (Barcelona) at beautiful sea-side spot at the sea-side as location for the meeting and a typical restaurant for the joint evening dinner on the first day of the WS.

Many thanks also go to the participants: Thanks to them, the meeting has been very enjoyable, informative and successful, with 14 major presentations, lively and fruitful discussions and clear decisions for the contents and schedule of the DoReMi TRA statement and final TRA, the position and policy papers highlighting the outcomes of the DoReMi project.

3. Actions to be taken after the meeting

1. After the consent of the participants, all ppt presentations will be brought on the DoReMi Website.
2. Dietrich will prepare a Report of the DoReMi TRA consensus meeting (this report)
3. WP leaders and WP task leaders are asked to check:
   3.1. Whether the sub-questions referring to the different WP and tasks are OK. This should help structuring the TRA statement and Final TRA.
   3.2. Whether their DoReMi publications were always well classified under the right WP and the right task (see Annex I and Annex II). Also, the sentences highlighting the main results should be checked and corrected, if necessary.
   3.3. New publications should be sent to DoReMi MB by stating to which WP and task they should belong to, and one or two sentences highlighting the main result obtained.
4. All Workpackage leaders start projecting their DoReMi WP position papers with informative illustrations (deliverables at the end of this year).
5. Dietrich is going to provide a first draft of a possible DoReMi statement (final version to be prepared for June 2015) and start work on the final TRA (to be delivered at the end of the year).