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## ToxAlim - Toxicologie alimentaire

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agence d'évaluation de la recherche  
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit

TOXALIM

From the

INRA

Ecole Nationale Vétérinaire de Toulouse

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Le Président  
de l'AERES

Jean-François Dhainaut

Section des unités  
de recherche

Le Directeur

Pierre Glorieux

May 2010



# Research Unit

Name of the research unit : TOXALIM

Requested label : INRA, ENVT, EIP

N° in the case of renewal

Name of the director : M. Bernard SALLES

## Members of the review committee

### Chairperson:

M. Robert BAROUKI, University Paris 5

### Other committee members:

M. Olivier LAPREVOTE, CNRS, Gif-Sur-Yvette

M. André GUILLOUZO, INSERM, University Rennes 1

M. Marc PALLARDY, University Paris 11

M. Bernd KAINA, University of Manz, Germany

Mme Barbara DEMENEIX, Muséum National d'Histoire Naturelle, Paris

M. Pierre MARQUET, INSERM, University of Limoges

M. Alexandre PERRY, INERIS, Verneuil en Halatte

Mme Yvette TACHE, UCLA, USA

M. Robert BAAN, IARC, Lyon

Mme Florence DOUCET-POPULAIRE, Hôpital Bécélère, Clamart

### Committee members nominated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

M. François SICHEL, membre du CNU

M. Patrick HILLO, membre des CSS de l'INRA



# Observers

AERES scientific advisor :

M. Pierre BEDOSSA

University or School representatives :

M. Alain MILLON (ENVT)

Research Organization representatives:

M. Patrick ETIEVANT (INRA)

M. Abdenour BENMANSOUR (INRA)



# Report

## 1 • Introduction

- Date and execution of the visit

The visit was executed on November 23<sup>rd</sup> and 24<sup>th</sup>. It started by a general presentation by the Unit head describing the history of this new unit and the general strategy. Then, each team presented and discussed its past achievements and its projects for approximately 1h (+/- 33% depending on the team size). Presentations per se lasted for half of the time and the other half was left for discussion. The committee met with local and national representatives and with the research scientists, technicians and students/post docs. Two internal meetings of the committee members took place to discuss the evaluation report.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

Toxalim is an ambitious project consisting of 10 teams originating from 4 units belonging to INRA, INRA/ENVT and INRA/EIP as well as a team from a CNRS laboratory. The original units are: INRA UR 66, INRA/ENVT UMR 181, INRA/EIP UMR 1054, INRA/ENVT 1089 and a team from CNRS UMR 5089. The unit is mainly located at two sites, at the INRA campus and at the ENVT campus. These campuses are relatively close to each other (5 mn drive or 5 mn walk if physical connection is improved!). The main focus of the unit is Food Toxicology in its broad acception, ie including work on food contaminants detection, metabolism, kinetics and action, on gastrointestinal tract physiology and pathology and on systems toxicology. The previous units were more specialized in one or more subfields and it was felt that the creation of a single larger unit would increase the ability of the teams to carry multidisciplinary integrative research with higher international impact and visibility.

- Management team

The unit is expected to have a Director, a general secretary and an executive secretary. It is run by an executive committee (coDir) which includes the Director, a general secretary, 3 appointed research scientists or professors and two elected members from the scientific committee. The management also includes a scientific committee which includes all team leaders as well as internal or external appointed members. In the opinion of the visiting committee it could also include additional external or even foreign members. The unit will also have a traditional laboratory council as well as several working groups for various items (equipment, scientific animation,...). The unit includes services and technical facilities with specific management committees. The administration will be under the leadership of a general secretary and will include seven persons.



- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	15
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	23
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	7
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	69
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	7
N6: Number of Ph.D. students (Form 2.7 of the application file)	18
N7: Number of staff members with a HDR or a similar grade	21

## 2 • Overall appreciation on the research unit

- Overall opinion

The Toxalim project consists in the creation of a large INRA unit (TGU) in Toulouse which should include 4 previous units as well as a smaller group from the university of Toulouse (IBPS, CNRS). The project is quite ambitious in that it aims at creating the only large research center in France dedicated to food toxicology. While this center remains smaller than other prestigious foreign centers in this field (notably in the Netherlands), it certainly represents one of the best possibilities in France to gather teams and platforms with complementary expertise in this particular field of Toxicology. Several members of Toxalim are involved in international expertise and collaborations. Despite some heterogeneity in the strengths of the different teams, the expertise of some of the teams is unique and, if strengthened, will give the center a wide audience in french and european toxicological sciences. The unit project consists in 10 teams addressing various aspects of nutrition and toxicology. There are several themes (cancer, metabolic disease, xenobiotic transport etc.) that are common to several teams originating from different units. Also, a few collaborative projects involve several teams which should enhance the cohesion of the unit; however, these common projects could have been highlighted more efficiently during the visit. The project includes the strengthening of local platforms in connection with other platforms in Toulouse (genotoul, metatoul). Some of the planned platforms are similar to other technical core labs in other centers, while others are relatively unique and should increase the efficiency and visibility of the Toxalim unit (analytical and metabolism platforms, large animal facilities). The teams constituting the unit are relatively heterogeneous in size, type of research and attractiveness particularly when basic research and classical bibliometric aspects are taken into consideration. However, even the smaller teams carry research projects that are in line with the INRA and veterinary school scientific goals in close interaction with the agricultural and nutritional economic partners. A specific issue is that the unit is located in two different sites.

- Strengths and opportunities

The major strength of Toxalim is that it will constitute the largest center for food toxicology research in France and will certainly become the leading center in this particular field. The Center should play an important role in the organization and renewal of French toxicology. Ultimately and if support for the Center is sustained, it could become competitive with other European centers in this field.

-There is a large multidisciplinary research expertise in the unit which should allow the implementation of ambitious research projects addressing the major issues in food toxicology, ie the effect of low doses and of mixtures. Some of the major strengths are the expertise in xenobiotic metabolism, OMICS technology, physiology and pathology



of the gastrointestinal tract, hormone action, PK-PD. The combination of these fields of expertise is essential for the quality of research that should be carried.

-In addition to research expertise, the unit includes experts in more applied aspects that are critical for the agricultural and economic fields related to animal and food safety.

-The project includes the implementation and/or strengthening of several platforms. Some of these platforms are unique and will be useful to Toxalim teams and beyond (metabolism, large animals, biostatistics).

-The leader of the Toxalim project is an excellent scientist with international visibility and a strong expertise in toxicology. This leader has been trained as a veterinarian and a scientist and is experienced in research unit management and teaching management. In addition to the head of the project the management of the unit will also involve three senior scientists. The INRA background of these scientists will be invaluable for the leader of the project.

-Several members of the unit are teachers in veterinary and agricultural schools. Many of them teach in Master and PhD programs in Toulouse and elsewhere. The scientists working in the unit are also involved in larger scale communication (press, radio and TV interviews as well as communications to the public).

- **Weaknesses and threats**

-There is some heterogeneity in the strengths of the teams constituting the unit. Some teams are either small or lack international visibility or have a modest publication record.

There is also some heterogeneity in the implication of the teams in food toxicology. Although all the teams stated their willingness to integrate the Toxalim unit, the projects presented by some of them seem to belong to other fields such as physiology, physiopathology and mathematics. Clearly the committee believes that such expertise would be very useful for food toxicology, but, at this stage, it is unclear whether all members of the teams agree with this.

While core facilities are a strong point for the unit, it was unclear for the committee whether all such facilities were required locally since the Toulouse area comprises several similar facilities. Specifically, while a transcriptomics facility is important for several teams of the unit, the interaction between this facility and génotoul were unclear to some members of the committee; however, the emphasis on biostatistics was appreciated.

- **Recommendations to the head of the research unit**

-The head of the unit is encouraged to take local, national and international action to strengthen the unit and to bring it to a competitive international level. Specifically, it is the unit interest to attract new and highly competitive teams if it wants to improve its international standards. This can be accomplished by providing space and support and possibly by an international call for candidates. INRA and ENVT could help in this respect.

-The committee approves the general structure of the unit based on teams and platforms which should catalyse a sense of belonging to the new Toxalim unit. However, the team heterogeneity may constitute a threat in the long term as similar quality and performance standards should be applied to everybody. One possible way to address this issue is to individualize "emerging teams" within the structure of the unit. Those teams would be smaller, with a project that is highly relevant for INRA but would have a few years to become larger and more competitive. It should be also possible to assign more methodological responsibilities to certain teams.

-The unit plans to develop several platforms which is excellent. Since this will be expensive and will require personnel, the unit is encouraged to prioritize the platforms it wants to develop preferentially. The committee felt that some platforms such as those dedicated to metabolism and large animals are not only useful locally but would contribute to increase the visibility of the unit.

-The unit head is encouraged to build interactive projects across the large unit. This has already started with success in some cases, but this should be pursued since it should help to foster the cohesion of the unit.

-Several positions have already been attributed by INRA to various teams and the committee believes that this is critical for these teams and for the unit future. In some cases (team 6 and 9), the projects of the new staff were not clear yet. The unit direction should critically assess the projects of the new staff in terms of quality and needs of the unit as a whole. The committee supports the recruitment of an INRA scientist in team 8, the team of the unit head.





INRA and ENVT are encouraged to facilitate the building of a physical connection between their two campuses.

- Data on the work produced :

(cf. [http://www.aeres-evaluation.fr/IMG/pdf/Criteres\\_Identification\\_Ensgts-Chercheurs.pdf](http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf))

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	36
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	
A3: Ratio of members who are active in research among permanent researchers $[(A1)/(N1 + N2)]$	36/38
A4: Number of HDR granted during the past 4 years	6
A5: Number of PhD granted during the past 4 years	34
A6: Any other relevant item in the field	

### 3 • Specific comments on the research unit

- Appreciation on the results

The research that has been developed in the units constituting Toxalim is in line with INRA and ENVT objectives. Several projects address animal health and food safety and have led to significant results. There is some heterogeneity between the teams. Some of the teams carry basic research projects and publish their papers in general or specialized journals with good impact. Other teams carry more applied research and generally publish their work in highly specialized journals (in fields such as veterinary sciences, pharmacokinetics, mathematics and even toxicology in general), with lower IF. However the latter teams do address issues that are critical for INRA and for its partnerships. Also, several scientists are recognized experts in those fields. While the originality of the projects is quite heterogeneous, it is expected that the gathering of teams that have complementary expertise (physiology, systems biology, mathematics...) should lead to original projects. The results obtained by the different teams have different types of impact, either in basic biology and physiology or in specific fields such animal health, drug metabolism and resistance...

The scientific production include 300 publications referenced, 185 conferences or seminars as invited speakers, 19 co-organisation of meetings, 34 thesis and 6 HDR in the last 4 years. The scientific output is good to very good depending on the team. As mentioned, some of the teams carry highly specialized research and can only publish their work in specialty journals. Some of the inter-team collaborative studies have proved to be quite successful (for example a PNAS paper in 2009 common to team 4 and team 1). Concerning invited conferences, the unit includes several scientists that are highly recognized for their research and expertise. These scientists are invited to international conferences. However, several of those scientists will probably retire within the next few years and it is important for the unit that younger scientists improve their international connections and visibility.

There is a strong interaction between some of the constituting units and food industries both in terms of food quality and safety. For example: mechanism of drug resistance, toxicity of veterinary drugs and of pesticide mixtures... Consequently several members of the unit are experts in national and international agencies. Again, this could still be improved and it is important that younger scientists get involved in such partnerships.



- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

This is highly heterogeneous. Some members of the unit are indeed invited to international conferences on a regular basis, while others are not. The constitution of Toxalim is expected to improve the general visibility of its members with time. Several members of Toxalim have been invited as experts in international and national agencies, sometimes with leading positions (including EFSSA, AFSSA, AFSSET...).

The unit has a good record in recruiting junior scientists with either INRA, ENVT or agriculture school positions. Several of those junior scientists have become group heads in the project. The head of the unit who is an internationally renowned scientist has joined one of the INRA unit one year ago. Conversely, there are relatively few post-docs and very few from abroad (5). Some of the teams have a good record in recruiting students while others could do better.

The ability to raise funds is a strong point for certain teams. Some of the teams have been very successful in raising funds from the EU (FP7), or the ANR as well as other agencies. The unit as a whole (based on the performances of the 4 constituting units) generated up to 1,000 k€ per year, which constitutes 2/3 of its funding (not including salaries of civil servants). There is some discrepancy between teams, but overall the constituting units were very successful. Several teams have projects that are relevant for industrial clusters such as animal production and drug safety. However, these aspects are part of INRA management duties.

Some of the teams participate in international networks (please refer to each team involvement). Possibly the creation of Toxalim will help other teams in their attempts to gain such international connections.

A few patents have been filed by some teams. The expertise in some areas of animal health and food safety is very useful to the food industry.

- **Appreciation on the strategy, governance and life of the research unit**

This is a project for a new unit, so the past management will not be evaluated. The project for the unit organization is sound and the governance quality as well as communication is expected to be good. While the task of bringing together 4 units is certainly challenging, the committee recommends improved internal communication so that all staff is well aware of the project details. The international experience of the unit leader will ensure a good external communication.

The leader of the unit presented several themes that are common to several groups. It is noteworthy that there are already several ongoing internal collaborations, some of them being quite successful. Such collaborations could have been even more highlighted. A major step towards integration is the constitution of strong platforms that are relevant to most of the Toxalim teams. This is a strong point for integration. In addition, part of the budget will be dedicated to new risky projects, however, little details were given. It is believed however by the committee that the constitution of Toxalim will have a positive impact on more ambitious and risky projects as compared to the previous situation.

This is a strong point for some of the teams (see below) as well as for the unit leader who has been the head of a very successful doctorate school (PhD program) for several years. The project of a European master in toxicology is an ambitious and worthy project, in the context of increased needs for such scientists and experts.

- **Appreciation on the project**

The general project of the toxalim unit is to bring together teams that are experts in food toxicology or related fields and to support the development of integrative methods in these fields (systems biology, PB-PK, integration of cell biology with physiological models...). In addition to this global project and to the specific projects of each teams, there are several collaborative projects in the field of toxicology: for example, the effect of Bisphenol A, of pesticides and their combination, of nuclear receptors, metabolism and kinetics... Some of these projects have already been funded. In addition, the development of platforms is an important step towards integration and support for smaller teams which would not be able to develop such sophisticated methodologies. Thus, in addition to the general scientific project, the unit will help in the development of useful tools.



In addition to the policy regarding the running of services and facilities, the unit plans to dedicate part of the budget to support new, risky and innovative projects that may not be easily funded by external agencies. This is a sound policy that will be more precisely implemented later on.

As mentioned, the unit will specifically support projects with risk-taking. It will also support projects involving several teams to foster the cohesion of the unit. The platform policy is an important part of this scheme. Again, since this is a new unit, one can only evaluate the future policy and not the achievements.

#### 4 • Appreciation team by team

**Team 1:** Integrative Toxicology and metabolism

**Team leaders:** M. Hervé Guillou and M. Pascal Martin

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	6
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	3
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The research activity of the team, essentially focused on nuclear receptors (NR), has favoured the development of « integrative » approaches based on cellular and animal models as well as transcriptomics, the latter facility being made available for the local scientific community since 2002. The metabolomics/lipidomics strategies, although mentioned in the document, remain at their premisses but are expected to play a more prominent role in the future.

As demonstrated by the list of publications involving external collaborations (22 out of 26), the expertise of this team is widely recognised at the national scale. In this respect, the preeminent role of the past leader, on leave to head the Animal Health of INRA, is highlighted by his invitations for a significant number of seminars and his involvement in many scientific committees.

26 articles have been published during the past four years, showing an excellent productivity with regards to the small size of the group. However only few of the published papers (4 out of 26) distinguish the team members as first, last and/or corresponding authors. A similar observation can be made from the oral communications list. This indicates clearly a research strategy based on the building up of a collaboration network at the expense of the internal research development. Four papers are collaborative studies with mathematicians. Only two PhD thesis are recorded during the past contract.



As mentioned before, a high number of fruitful collaborations testified by published papers is one of the strenght of the team.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

Two invitations at international conferences in foreign countries are noted for the past team head in 2006. No prize nor distinction is mentioned for the past period. However, the nomination of the past team director as head of the Animal Health of INRA can be considered as a mark of recognition by the INRA institution.

The number of master-level students is significant. By contrast, there is a clear lack of PhD students (2 currently) or post-docs (1 arriving in Oct 2009). Two recruitments are to be noticed, one permanent researcher and one engineer.

A good number of grants have been obtained, in particular from INRA projects but also from ANR (1 granted project). It demonstrates a dynamic activity to raise funds from research institutions.

Some international collaborations (3) demonstrated by common publications or grants are mentioned, the stability of which being difficult to evaluate.

- **Appreciation on the strategy, governance and life of the research unit**

In such a relatively small group, the role of the past team chief as head of the lab was central. There have been some retirements or departures that were balanced by equivalent recruitments without any visible destabilization of the scientific activity. The investment of the past head of the team in external communication is noteworthy with many interviews in the public press or in the TV.

As indicated above, the research activity is organized within a wide collaborative network. Some of them are led by the team, in particular an international INRA-FORMAS project (2009-2010) and an ANR project.

The involment of the team members in teaching activities is characterized by the participation in a high number of master formations but with a limited intervention time except a 12 hours course of P. Martin at the University Paul Sabatier (Toulouse). The latter is an interesting opportunity for the recruitment of future PhD students. Besides, the involvement of this team in the local organization of research is expected to increase in the favourable context of the Toxalim unit creation.

- **Appreciation on the project**

The medium-term scientific project is in line with the past activity of the group and in agreement with the Toxalim unit structuration. Technically, the transcriptomic approach will be strengthened owing to the development of the TriX transcriptomic platform dedicated to both targeted and high-throughput strategies. Similarly, the data treatment and data mining issues will be adressed within a well-established collaboration with biostatisticians (GenoToul biostat platform) and mathematicians (Institut de Mathématiques de Toulouse).

Globally, the majority of the project items are scientifically sound and will not be commented on further here. However, the following threats will have to be taken into consideration. First, the management of the team which will be led by two young researchers is an important issue. This two-head direction appears inappropriate regarding both the size of the group and the global research project (who will decide of what?). The team ability to completely master its ambitious project is also problematic, taken into account the presence of only two permanent researchers within the group (without HDR at the time of the evaluation) and two engineers and the necessarily low number of expected PhD students (only one would work full-time for the group and 2 others are co-directed in a collaborative context).

Second, one particular aspect of the project relies on lipidomics and metabolism. There is no clear indication (from the written project and from the oral presentation) on the way by which lipidomics studies will be performed. Similarly, the aspects related to the endocrine disruptors (*e.g.* bisphenol A) and metabolomics approaches should have led to explicit interactions with the team of D. Zalko and with the Axiom-MetaToul platform. The lack of such collaboration between these two teams is likely to be detrimental to the credibility of this part of the project. Conversely, if such a collaboration is strengthened, the prospects for this part of the project would be very much improved.



Finally, the long term project dealing with the nuclear receptor interactome appears to be speculative, partly out of the scope of the teams' know-how, and insufficiently justified in view of the local technical facilities or expected collaborations.

Despite the enthusiastic involvement of the two young leading researchers, there is no clear strategy in terms of resource allocation. As in the past period, the majority of the project is based on a strong collaborative network. It is probably the best choice for such a small team in the short-term period but it does not give any indication about the middle- and long-term management of the scientific policy of the team.

Globally, the project is in accordance with the field of expertise of the team. Some new aspects are scientifically relevant whereas others are not fully convincing. Among them, lipidomics and NR interactomics are not risky by themselves but by the lack of truly documented feasibility evidences.

- Conclusion

- Overall appreciation

The Integrative Toxicology & metabolism (TIM) team is scientifically active, dynamic and well-recognised for its expertise on nuclear receptors. The publication rate is excellent and shows a high number of fruitful collaborations with national and international laboratories. The articulation of the past and new research projects is relevant while maintaining the Nuclear Receptors as the guiding thread. The creation of the Toxalim unit offers this group an excellent opportunity to develop its own research program provided that convenient collaboration agreements with other local teams are truly established. Some weaknesses in that respect make the chance of success of some items of the research project doubtful. In view of the strong personal involvement of the two young leaders and of the (too) ambitious research program of this group, the team should be encouraged and strongly supported by the Toxalim Unit and the INRA authorities.

- Strengths and opportunities

- Good to excellent publication level in the past period.
    - Energy and ambition of the young team leaders.
    - Credibility of the expertise in the NR field.
    - Rich and numerous collaborations with national and international groups.
    - Increased opportunities to collaborate locally owing to the Toxalim unit creation.
    - Relevant evolution of the research topics towards "applied toxicology" and xenobiotics metabolism in the context of Toxalim.
    - Further development of the TRIX transcriptomics platform and of the relationship with the "Biostat" platform.

- Weaknesses and threats

- The management of the team by a pair of young researchers, even individually excellent, is not appropriate for such a small group.
    - The research project is too large with regards to the human resources of the team.
    - The difficulties associated to some of the omics approaches, from both academic and technical viewpoints, are underestimated by the authors.
    - The research policy in terms of collaboration vs. own research development and of financial funding is not sufficiently clear.



## – Recommendations

We suggest the team leaders to decide in favour of another team management scheme leading to a more clarified decision-making policy.

The team is encouraged to continue to develop and invest in its expertise field (NR), as shown in many respects in the research program. The new research axes are in majority relevant but some of them could be made more credible through stronger interactions with other local groups (*e.g.* team 2) and platforms. In that respect, we suggest to create explicit links between the TRIX and the Axiom-Metatoul platform, which together represent one of the main strenght of the Toxalim Unit.

The committee recognizes the importance for a small-sized group to interact with other groups. However, this strategy should not be detrimental to the internal research development. The team leaders are thus prompted to pay attention to the balance between the external/internal research projects. In that respect, the recruitment of PhD students is of primary importance.

### Team 2: Metabolism of Xenobiotics

Team leader: M. Daniel ZALKO

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Over the last four years, the “Metabolism of Xenobiotics” (MeX) team have conducted a coherent research program on:

- the transfer of contaminants along food chains.
- metabolic pathways of food contaminants (particularly bioactivation pathways).
- characterization of their metabolites (particularly those produced at sites of toxicity).
- the links between biotransformation and toxicity.

-more recently, metabolomics and metabolic networks as a way to identify biological perturbation in response to toxic compounds.



They applied this research to:

-the plasticizers bisphenols and metabolites, as models of endocrine disrupting chemicals (EDC), as well as bisphenol A as a probe toxicant for the metabolomic approach.

-brominated flame retardants (BFR) and metabolites, and their transmission from mothers to newborns.

-PAH and metabolites and their relationships with markers of genotoxicity.

The team has a national and probably an international visibility in the first two application fields at least.

Members of this team are frequent users of the AXIOM-METATOUL platform, with which they also have several research projects in common.

There are 64 papers and reviews referenced with an impact factor, which is very good for a small team. However, many of these papers were in collaboration with other teams, and the number of papers with an IF > 3 where team members were in the first three or in the senior author positions is much smaller.

14 communications with published abstracts, 14 other oral and 53 poster communications in scientific meetings are mentioned with 1 book chapter and 4 theses during the past 4 years. 8 invited conferences (of which 2 in English) and 9 dissemination conferences or interviews have been given by the team members to general media (TV, newspapers, etc.).

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The team has trained 6 PhD students and 2 post-doctoral fellows in the past four years. However, only one post-doc and no PhD student is listed in the team under its new configuration. In 2011, 3 post-docs will join the team in September, within the frame of ANR Nistec (12 months) and EU FP7 People Cofund program 246553 "CASCADE FELLOWS" (2x12 months). Moreover, at least 2 PhD student should be listed.

The ability to raise funds is excellent. They have participated in one EU-funded project (CASCADE Network of Excellence. EU/FP6, 2004-2010), obtained (or have participated in) 7 ANR contracts, 11 other national research contracts, and obtained regional funding for one project and private funding for another one.

There are collaborations with 8 different teams in Europe (Spain, Norway, Sweden, The Netherlands, UK) and North America (USA, Canada), 4 of which resulted in common papers (in journals with a good impact factor) and 1 in common oral and poster presentations.

The research activity and the team expertise and findings had have important impact of on the opinion, through the (mainly French) media.

- **Appreciation on the strategy, governance and life of the research unit**

This group is a small team with apparently good collaboration and complementarity between members. Team meetings held each week.

In term of emergence of cutting edge projects and initiatives, the team members were among the first to study the plasticizers bisphenols and metabolites, and brominated flame retardants and metabolites, which were revealed to be important public health issues.

Four unit members have teaching activities, mainly at the M2R and doctoral level, not only in France but also in other European countries (Ireland, Portugal) or for European teaching programs (BIOCOP CASCADE European School, with teaching in Italy and France).

- **Appreciation on the project**

The team will essentially develop the same three main topics addressed in the last period, with an emphasis on human exposure and toxicity. In particular, they will develop new cellular models derived from human tissues and will determine the toxicants of interest and their biomarker metabolites in human samples. The committee thinks that this translation to human models and "clinical" studies will be essential in the context of the "big unit" to come.





They intend to reinforce the study of the mechanisms of action of probe toxicants, and the metabolomic/metabonomic approach they developed lately. They will also develop a new strategy to characterize

endocrine disruptors in complex mixtures, namely affinity extraction by ad hoc affinity columns, as well as imaging techniques to localize toxicants and metabolites in target organs. This evolution towards innovative technical or methodological approaches is a real challenge for the team, but one that may be rewarding if successful. Affinity extraction has the potential to be a good complement to the team's tools, but the corresponding project about it is still rather vague.

In addition to BFR, plasticizers and PAHS, the team will also study pesticides, although to a lesser extent apparently. The team also envisages selecting other families of toxicants, but they do not explain on which basis. The committee would recommend keeping the same three families of toxicants to begin with, while adapting to the new models and techniques.

The project originality lies in the new methodologies the team will employ and their application to human models or samples.

- **Conclusion**

The research program is coherent and original in continuity with the team achievements during the previous period. This team possesses a real expertise in the metabolism of toxic compounds and had a very good scientific production over the last four years.

- **Strengths and opportunities**

- The team will play a central role in the future large unit.
    - The project presented to the visiting committee was coherent, and more precise than the written project.
    - During the previous quadrennial period, the team published many papers, of which a lot in collaboration.
    - They obtained many contracts and grants, and conducted or participated in national and international collaborative projects. The team is already engaged in new collaborative research projects with international teams.
    - One researcher is very frequently interviewed by national and international media on safety issues.

- **Weaknesses and threats**

- Not many papers with team members in the first three or in the senior author positions and with high IF.
    - Not many invited conferences, but maybe under-reported.

- **Recommendations**

- More team members should pass the HDR.
    - The team should train more PhD students.
    - The team should try and increase their international visibility and attract more international students, post-doc or invited researchers/professors.





### Team 3: Endocrine Disrupting Pesticides

Team leader: Mme Catherine VIGUIE

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

This team currently addresses a topic of major relevance to the TGU, that of endocrine disruption. The group has shown a rather low productivity over the last four years, with only five papers published in journals of modest to medium impact during this period (see below for details). However, this rather low productivity can be attributed to two factors that have changed, and are now behind them.

First, the small size of team has to be taken into account, with only one full time researcher and two university professors, each with significant teaching duties. Further, it is mentioned in the report, that up until March 2009, no technical staff was attributed to the team, or only on part-time basis. This situation has changed with the appointment of a new 'Ingénieur' (IE2).

Second, the team has had to adapt over the last three years to a major change of research focus. The team has switched from its principal focus, prion disease-associated neurodegenerative disease and the endocrine pathologies (mainly corticotropic and somatotropic axes) linked to these diseases to that of endocrine disruption (ED). Over the last three years they have introduced and obtained funding for a totally new research area. Thus, for the past contract period this small team has been tackling the difficult task of concluding one research program previously considered high priority by INRA and opening up a new one. Now, the researchers, again in consultation with the different levels of management, have decided to make ED their main research area, concentrating on disruption of two endocrine axes: thyroid and reproduction. Proof of principle has been obtained in the context of a PNR -PE grant (co-ordinated by the team leader) on the action of the pesticide fipronil on thyroid function in sheep.

Five publications appeared during 2005- 2009, plus one under review at time of submission of project in:

*Toxicology, Br J Pharm, Transfusion, J Gen Virol, Dom Animal Endoc.*

Only one of these (Toxicology) reports results on the new research area, that of endocrine disruption, as the team only moved into this field in 2006. Four contributions to university textbook chapters were made in the same period.



- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The team leader is currently investigating the possibility of bringing in a top-level scientist to collaborate on the the endocrine disruption theme.

The team obtained two grants in 2005-8, both from national funding programs (PNRs). These grants are on the new topic of endocrine disruption and underline their credibility and recognition in these domains.

As mentioned above the team is involved in national networks through the national funding programs that bring together different laboratories.

- **Appreciation on the strategy, governance and life of the research unit**

The team is small , but well organised.

This group has certainly shown its willingness to take risks and to enter into new fields. Furthermore they have shown their capacity to finance successfully these new endeavours and must be encouraged in these new fields.

Two of the three team members have significant teaching responsibilities in the Vet School. Two PhD students are currently being formed in the team.

- **Appreciation on the project**

In the next four years, the team aims to address pituitary function (in particular, TSH and LH production and secretion) as potential targets of endocrine disruption (ED).

It is proposed to address questions framed within the following axes :

toxicokinetic evaluations of the toxicants in the model species and validation of these models for the physiological scheme of regulation of the studied functions.

Once these animal and cellular models have been validated, to apply modelling approaches and PK/PD concepts to characterize the actual exposure (i.e blood concentration) / endocrine disruption effect relationship so as to evaluate risk for human health of the characterize (known) human exposure.

Mechanistic studies of ED action investigated at all levels from the genome to the in vivo whole animal.

However, needless to say, this spread of questions and methods applied to TWO endocrine axes seems too much for such a small team and again a choice has to be made. Even though, the team leader has excellent experience and knowledge of pituitary function and the large animal models (e.g. sheep), the proposition to exploit this know-how to examine how certain pesticides and other pollutants eg BPA affect these two axes is over ambitious. It would be far wiser to concentrate on one of the two. For a number of reasons, notably, potential interactions with other teams, better use of the team's increasingly rare capacities to work on large animals with radioactive tracers, a wise choice would be to focus on endocrine disruption of the thyroid axis. Such a focus would again fit with national/international priorities and a number of socio-economic considerations.

As mentioned above the team is original in the national and interantional arenas of endocrine disruption by their knowledge and use of large animal models. They have clearly shown their capacity to take risks and bring new reseach themes to successful conclusions.

- **Conclusion**

- **Overall appreciation**

This small team has a number of original approaches, knowledge and skills, particularly in the area of thyroid physiology that are increasingly rare on the national, particularly INRA, research scene.



### – Strengths and opportunities

Clearly it is essential that a small team, with strengths in their in depth knowledge of physiology and endocrinology coupled with access to increasingly rare techniques (eg use of radio-isotopes on large animals for turnover studies) make best use of their important skills. One means is to interact efficiently with other teams on the site. It is reassuring to see that this already appears to be the case. Indeed, the team's new projects will provide a number of potential interfaces for collaborative work in the new TGU.

A modelling approach is to be developed in collaboration with team 7, placing emphasis on common expertise in PK/PD methods. Fruitful interactions are also being developed with team 1, notably in the field of nuclear receptors ( TRs and potentially PPARs).

It would seem that certain aspects of the project require the expertise of Team E2. These collaborations should be strongly encouraged, given Team 2's expertise in metabolism, a key aspect of endocrine disruption.

### – Weaknesses and threats

The rather disappointing performance of the team can clearly be attributed to past weaknesses that have been resolved. Obviously, as it stands, the team, despite its unusual and important palette of competences, is not of sufficient size, nor strength, to be competitive. This situation requires discussion and reflection as research on thyroid function and disruption in France is seriously losing momentum.

### – Recommendations

One recommendation could be that their expertise on thyroid disruption should be pursued and developed in the Toxalim unit either through their recognition as a small « emerging team » or within a larger team focusing on endocrine disruption or metabolism.

## Team 4 : Neuro-Gastroenterology and nutrition

Team leader: Mme Vassilia THEODOROU

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5+1 recruited in 2010
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	14	12
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	6
N7: Number of staff members with a HDR or a similar grade	6	6



- **Appreciation on the results**

Neurogastroenterology and Nutrition is the largest of the 10 teams and has a long standing history of strong leadership and pioneer contributions in the fields of basic research on gastrointestinal physiology of motility, neural and immune interactions, probiotics, brain-gut interactions in relation with motility disorders, functional bowel diseases and colonic inflammation. The present focus of the team is the neuro-immune regulation of intestinal barrier function by endogenous mediators and factors present in the gut lumen. Such a team is relevant to the overall objectives of TOXALIM in relation with the studies of commensal flora, probiotics and influence on intestinal barrier integrity.

The team has sustained excellent productivity since 2005 with 45 peer reviewed articles, 31 of which are coauthored by research directors. Those articles are published in well respected journals in the gastrointestinal and neurosciences field, with several appearing in high impact factor journals (Gastroenterology, Gut, Pain, Neuroscience). They have also contributed 17 authoritative reviews in leading peer review journals on the etiology and pathophysiology of functional bowel disorders, gut permeability and motility. In addition the team had 39 oral communications along with 59 posters presented at national and international meetings. Therefore this represents an excellent visibility and output of the team during the last four year period. . In addition one of the group leader held several patents in licensing since 1977 and recent one treatment of IBS and IBD

The team has a long standing history of efficient partnership between the previous two unit directors. In addition, previous leadership has developed a team of mature investigators who had productive interactions for a decade. The new leadership, Dr. V. Theodorou has been working for the past decade with the previous leadership showing the stability of the partnership within the groups. In addition to internal partnerships, the unit had successful partnership with industries through out the years including Jouveinal and others that lead to scientific contracts supporting the trainees.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners:**

The unit has throughout the year trained many international postdoctoral fellows from Europe (Spain, Greece, Bulgaria, Scotland, Poland, Holland, Hungary), as well as the USA, Australia and China, showing the visibility and attractiveness of the research unit. They also established a collaborative link with the Department of Physiology and Pharmacology, University La Sapienza in Rome (Publication # 36), the Parasitology Laboratory, and Institute for Biomedical Research, University of Rouen (publication # 44) and other laboratories that resulted in joint publications.

The pioneered contributions to our understanding of neuro-immune regulation of intestinal barrier function, visceral pain and underlying mechanisms of functional bowel diseases made by the team are well recognized internationally as shown by 61 national and international invited conferences with a high visibility of previous research directors. In addition there were 59 oral communications at annual national and international society meetings made by members of the team. Those oral communications reflect selection process of top abstracts submitted and therefore recognition of the research work generated by the team members. The leadership role of the team in the field of neurogastroenterology, motility and gut epithelium is also exemplified by the 3 national and 1 international symposia organized in Toulouse by previous and present directors. One of the team leaders received several distinctions including the Janssen Award from the American Gastroenterology Association, being the President of the French Gastroenterology Society and serving on the editorial board of several international peer reviewed journals.

The team has an excellent track record of attracting a number of graduates and national and international post-graduate students, a number of which thereafter have developed into well established investigators. There was no recruitment at other levels.

The team has strong ties with the French Motility Club, French Society of Gastroenterology and the Club d'Etudes des Cellules Epitheliales Digestives and a number of pharmaceutical companies involved in probiotic, and drug development for visceral pain.

- **Appreciation on the strategy, governance and life of the research unit**

The unit organization encompasses the previous directors who created the unit and have high international visibility and track record of contributions along with a mature group of established investigators who have complementary expertises in distinct topics and approaches. The team is going through a transition in leadership with another researcher becoming the new team leader in 2010 when actual leader is stepping down. The next group leader is well positioned to lead the team as she has been working for a decade within the group, and therefore



familiar with the administrative issues. She previously took leadership role in organizing two meetings in Toulouse in 2005 and 2006. She is a dynamic and effective communicator and well positioned to take such responsibilities.

The Involvement of the unit's members in teaching activities is not addressed in the documents or at the site visit. However the number of master and PhD students trained and being trained in the team indicates a excellent involvement in teaching at this level.

- **Appreciation on the project**

The medium- or long-term scientific project was not addressed at the site visit presentation that dwells on the historical development of the unit along with past research contributions by members of the team. Based on written documents, the research projects centered around the intestinal barrier function will be focused on three axis: the endoluminal factors (proteases, probiotics, flora), the neuroendocrine axis (estrogens), the viscerovisceral interactions (creeping fat, gut-liver). The feasibility of the projects as described are well in the range of expertise of the investigators and represent largely a direct extension of previous research projects by the team. In addition, there will be new project through interactions with team 1, in particular the gut liver interaction that is well supported by preliminary data. The bisphenol A exposure in utero and neonataly on immune bacterial response or development of colitis will be also relevant topic overarching TOXALIM objective. The last project related to axe 4, "soy isoflavone profile, level and expression" is much less developed, this along with project leader low previous contributions to this field cannot preclude the outcome of the project.

Although resource allocation policy was not alluded during the site visit, the team has a track record of publications on each of the three axis mentioned above suggesting a consistent resource allocation. Of note, one researcher of INSERM, U563, Centre de Physiopathologie de Toulouse Purpan, which is not part of TOXALIM team has a relevant productive program on Protease-activated receptors as drug targets in inflammation and pain, it will be important that some resources allocation are not devoted to duplicate similar objectives on PAR-4 running in this researcher lab. and that collaborative effort on this specific field be promoted.

Several aspects of the projects are novel and addressed important objectives particularly the proteases and flora actions on intestinal barrier and impact on viscerosensitivity which are timely as well as the complex role and actions of estrogen on the intestinal barrier which are still controversial and not thoroughly explored. The methodological approaches for most of the projects do not represent risk-taking.

- **Conclusion**

- **Overall appreciation:**

The team 4 of Neuro-Gastroenterology and Nutrition has an historical track record of outstanding productivity, creativity and national and international visibility in their field of investigation through the previous leadership. It is presently composed of large number of matured investigators who have experience of collaborations and are well positioned to develop the proposed projects of modulation of intestinal barrier function by microbiota, endoluminal factors, estrogens and oral bisphenol A. The proposed approaches are well in the expertise of the team which will also benefit of interactions with other teams and expertise in the platforms to expand the depth of their analysis using metabolomic and transcriptomic approaches.

- **Strengths and opportunities:**

The strengths relate to 1) the track record of the team with regards to the productivity, previous pioneer contributions in neuro-gastroenterology; 2) the well defined research program that is relevant to the overall theme of TOXALIM; 3) the international visibility as shown by invitations to meetings, recruitment of international post doc, publications in international high impact factor journals; 4) the composition of the team with a relevant blend of mid-career and more senior researchers along with the large number of Ph.D students and post doctoral fellows; 5) the interactions between other academic centers and with industries to perform translational research; 6) the beneficial impact to joint TOXALIM to be able to interact with other teams/platforms to gain access to novel technologies and methods of approach.

- **Weaknesses and threats:**

Those related to 1) Axis 4 project not well developed and lead by an investigator with a lesser track record of productivity; 2) Transition in leadership with presence of ex Directors with high profiles that can be an asset and/or



overwhelming to the ability of a more mid career new Director to lead the group; this was exemplified by the presentation at the site visit in which no handouts were presented, the lack of compliance to the time allocated for presentation/discussion, and only focused on past accomplishment without information on projects to be developed; 3) the clear focus on functional bowel disorders as a primary end point which is historically what the team is internationally known for, and whether the team as a whole will refocus to make breakthroughs in the field of alimentary toxicology or rather pursue their successful field of research in functional bowel diseases.

– Recommendations:

1) To strengthen the visibility and decision making to the new leadership.

2) To enhance interaction with other partners of the Unit who have historically devoted their research to food toxicology to assess impact on barrier function.

3) To strengthen the 4<sup>th</sup> transversal axis related to the determination of the profile, level and expression of phenolic compounds in raw vegetal material and food matrices.

Team 5: Immunomycotoxicology

Team leader: Mme Isabelle OSWALD

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0,5
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

This team has a well-recognized experience in the field of mycotoxin toxicology in the context of food safety with special emphasis on the immune system of the gut. Their research concerned mostly animal food safety but their results can also be extrapolated to the human situation. It is important to note that mycotoxins represent an important animal and human health problem since most of the cereals produced in Europe are contaminated with these toxins. During the 2005-2009 period, the team focused its work on the toxicogenesis of mycotoxins identifying biosynthetic pathways in the plant and on toxicity of mycotoxins on pigs through three main axes: effect on the gut, the immune system and liver biotransformation. To note, their contribution to the comprehension of the effect of mycotoxins on immune responses with links related to animal vaccination and infections. This team is leader in this field in France.

The team published 32 papers in international journals (1,4 per year per researcher) in the field of toxicology, veterinary sciences, nutrition and microbiology. Publications in veterinary sciences were mostly in the best journals of this field: *veterinary research*, *veterinary parasitology*. Publications in toxicology were in very good to good journals of this field: *toxicology and applied pharmacology*, *toxicology*, *toxicology in vitro*. The team is also contributing to



numerous book chapters on mycotoxins. However, there is no publications in more fundamental and higher ranked biology journals.

Six PhD thesis have been defended in the laboratory since 2005.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The team leader is regularly invited to international conferences (18 since 2005). Overall, the team has contributed to 30 invited international conferences and has also contributed to the organisation of 5 scientific meetings or sessions including one Gordon Conference. Members of the team are also heavily involved in reviewing activities (scientific papers, 3 editorial committees, grants).

Foreign PhD students are present on a regular basis for duration from 3 months to 18 months in the context of international collaborations (5 from 2005). Two foreign professors will be present in the laboratory for 2 years and will participate to the project (One from Brazil, one from USA).

Ability to raise funds is a strong point of this research laboratory. Team is involved in three european project with the team leader coordinating a WP in each of this project and has obtained 4 ANR grant since 2005 (CES, GENANIMAL, PNRA). The team has also obtained or is involved in other national grants (AFSSET, ADEME, RARE minister of research).

The team has strong links with foreign partners in the context of the european project cited above. They have also other collaborations with Canada and Brazil. They are involved in several network: Tournesol, ECO-NET, COFECUB, BRANCUSI, EFSA network).

The team is highly involved in the field of expertise for national (AFSSA) and international agencies (EFSA).

- **Appreciation on the strategy, governance and life of the research unit**

The team has been recently reorganised with the retirement of the former head of the group, the arrival of a new INRA CR1 and the departure of an INRA CR1. The team leader showed a strong project, well organised and based on a large network of international and national collaborations. The team leader has also a real visibility in her field of expertise and has proven her expertise for in raising external funding.

The activity of these past years has concerned several areas: toxicogenesis of mycotoxin and the effects of mycotoxins on metabolizing enzymes, the intestine and the immune system. This approach was quite broad necessitating different expertises that are always difficult to cover. Despite a good productivity, a more focused approach is needed for the future.

The team has recruited one assistant professor in 2009. However, most of the members are involved in teaching at the graduate and undergraduate levels including INRA researchers and engineers. 8 masters, 3 engineers and 6 PhD have been trained in the laboratory since 2005.

- **Appreciation on the project**

For the next period, the team has decided to develop its project on the co-contamination between major and emerging mycotoxins with a special emphasis on fusariotoxins. The goal of the project is clear with focus on the characterisation of mycotoxin toxic effects on the intestine of farm animals. To this extent, they will address specific issues dealing with the interaction between dendritic cells and intestine epithelial cells and the effect of mycotoxin on this interaction. One original approach is to perform a global transcriptomic approach in vivo on intestinal layers using laser microdissection. Chemical analysis will also be performed on the emerging mycotoxins. This project will benefit from the Toxalim platforms and also with the environment of other teams of Toxalim.

The project as presented is original and will certainly significantly contribute to the understanding of mycotoxin toxicity on the intestine and the consequence for the health of farm animals. The in vivo transcriptomic approach using deoxynivalenol and microlaser dissection is clearly a part that could bring major breakthrough in this field, however the expertise is not yet been clearly identified in the group but existing collaborations are listed. Characterisation and production of "emerging" fusariotoxins is long-lasting project and could lead to a low productivity due to lack of interesting results. However, it is important that this kind of project could be developed.





- Conclusion
  - Overall appreciation

This team is one of the scientific leader in this field with an international visibility and very strong interactions with agencies and the socio-economic world.

- Strengths and opportunities

Team well integrated in national and international network.

The scientific project is original, more focused than the one developed in 2005-2009 and strongly based on the expertise of the team.

Good ability to attract young researchers and foreign collaborators.

- Weaknesses and threats

The team needs to develop strong collaborations to ensure the success of the transcriptomic project.

- Recommendations

The team should consider publishing their work in more fundamental journals of broad interest to the community.

Increase their interactions with other Toxalim teams.

**Team 6:** Membrane transporters and resistance

**Team leader:** Mme Anne Lespine

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1+1 recruited in 2010
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	2	1

- Appreciation on the results

This team has been working on the pharmacokinetics and the activity of anthelmintic drugs, especially Macrocytic lactones (MLs) for several years. This research is part of the scientific strategic scheme of INRA Animal Health division. The team's research projects concern an important field in veterinary medicine. The number of research units working in this area is limited worldwide. Their works on Pgp were extended to the screening of





potential Pgp inhibitors, their in vivo validation and to in silico modelling of Pgp inhibition (with possible developments leading to the design of selective inhibitors). The most important application, of which the proof-of-concept has already been provided by the team, is the possibility to restore sensitivity in resistant nematode strains by means of Pgp inhibitors.

The number of publications within the past 4 years is satisfactory for a small team (32 publications, of which 13 directly relevant to the unit research program, and one licence deposit). The impact factors are among the best in the disciplines of veterinary sciences (2) and parasitology (2).

In the field of veterinary antiparasitic therapy, the team collaborates with local, national and international teams.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners.**

The group is visible at the international and national levels, as shown by seven and one invited conferences, respectively.

The contribution to the teaching of students is satisfactory with 2 PhD and 1 HDR in the past 4 years.

The team participates to one European project, 2 ANRS and regional projects. It is part of different national and international networks, e.g. of the European Research project PARASOL. They organized two meetings and chaired sessions in other meetings.

The team is involved in the field of expertise in veterinary medicine for national agencies. They organized international and national seminars for industrial partners and technical institutes on veterinary antiparasitic therapy.

- **Appreciation on the strategy, governance and life of the research unit**

The team leader has received instructions from INRA which seem to be somewhat at odds with the expert committee recommendations, and this will not help her clarify the team project, assign the newcomer a research program and reorganize the team organization chart in case of a fusion with another team.

The 2 researchers of the future team are involved in teaching. They participate to master degrees in Veterinary and engineer Schools.

- **Appreciation on the project**

The research projects centered around the multidrug ABC transporters will be focused on three axes :

The study of the numerous multidrug ABC transporters, their nature, fonction, regulation (in collaboration with team # 1) and their interaction with MLs or pesticides.

The influence of transporters on the bioavailability of drugs especially their role in the mechanism of resistance to antiparasitic drugs or insecticides in nematodes or insects.

The potential link between weight disorders and ABC transporters, including the influence of lipids on the transepithelial transport of xenobiotics and the role of pgp in lipid disorders. This is a new project.

These topics will be studied in collaboration with many different teams nationally and internationally (Pr Prichard, Montreal). They will use the in vitro, in vivo and molecular tools they have developped to study antiparasitic Macrocylic lactones.

While these different projects are of interest, they seem to be too ambitious for this small team. A more focused approach would be more realistic.

There is no clear ressource allocation policy.

The last topic on the link between weight disorder and ABC transporter which can be regarded as risky, will be complementary of those of team 3 on endocrine disrupting pesticides.



- Conclusion
  - Overall appreciation

The team has an expertise in the behaviour of antihelmintic drugs in host organisms of agronomic interest. The planned research program on this topic appears to be a logical step forward from previous studies in the TOXALIM context.

- Strengths and opportunities

Tools developed for research on membrane transporters and efflux pumps.

Relevance of the work on anti-helminthics to the animal production field.

- Weaknesses and threats

This team is one of the smallest teams of TOXALIM, with only one researcher (the leader) as well as one engineer. A position on a defined and published profile is opened and a new researcher will be recruited in June 2010.

The planned research program appears to be a logical step forward from previous studies in the TOXALIM context. However, different projects are planned, some of which are new for the team, and their number is hardly compatible with the number of researchers.

- Recommendations

The team should focus on transporters and antiparasitic drugs, and in the parasites rather than in the hosts.

Owing to the small size of the team, working on three different themes may not be reasonable.

A strong collaboration or even a fusion with another team could be considered.

### Team 7: Pharmacokinetics Pharmacodynamics and Modelisation

Team leader : M. Alain BOUSQUET-MELOU

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3+1 to be recruited
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	3
N7: Number of staff members with a HDR or a similar grade	3	3



- Appreciation on the results
- Relevance and originality of the research, quality and impact of the results

The question of antibiotic resistance is a major issue in Public Health. The orientation of the research project is original and corresponds to INRA requirements as stated by the "lettre de mission" for the head of the previous UMR 181. The mathematical developments are of interests not only for general toxicology but also for more academic research in mathematics. Consequently, one of the members of the team has been promoted professor of statistics at Paris Diderot University. The high level of collaborations with industry and agencies illustrates the practical interest of the research which is developed.

The publication rate is approximately 10 per year, which is a good level of publications, especially at the interface between biology and mathematics. Impact factors are among the best in the disciplines of veterinary pharmacology (around 2); antimicrobial chemotherapy (around 3) and biostatistics (around 1). There is still a small number of PhD students (1.5 per HDR for the past and 1 per HDR for the future period). This was already pointed by a previous evaluation in 2006 with no significant improvement, due to difficulties to attract veterinary students or to motivate future researchers in the field of veterinary pharmacology.

Relative to antimicrobial resistance, the team collaborates with a few local and foreign teams and an agency on resistance. This partnership seems to be stable, at least locally, and relevant. Relative to biostatistics, the team collaborates with an emergence team on clinical pathology. This partnership is stable, and the relevance stems from the use of the same statistical methods in this field as in the case of a TK/TD project applied to veterinary antibiotic therapy. The team also collaborates strongly with the Math Institute of Toulouse, in particular relative to statistical methodology for the analysis of "omics" data. This collaboration seems stable and is the only way to follow and contribute to developments in this field.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

There has been 15 invitations for international conferences during the past 5 years for 3 researchers of the team. However, the invitations of the past three years only concern two persons.

As stated before, there is still a small number of PhD students (1.5 per HDR for the past and 1 per HDR for the future period) and none from abroad. There was no post-doc in the past 4 years.

The team has a great ability to raise private funds, from pharmaceutical companies (money and thesis) and start-ups. They were also able to raise local funds, and participated in 1 ANR project (ATLAS).

There has been international collaboration on PK/PD for antimicrobial agents with partners in Europe and North America.

- Appreciation on the strategy, governance and life of the research unit

The team seems to be split in two parts (biostatistics and antimicrobial resistance) with no clear link between them, neither for the past years nor for the project. We note that the team was presented by two project leaders, one for each axis. The fact that these two leaders are the former head and deputy-head of the UMR 181 is not sufficient to justify this choice. There was more collaboration between the previous biostatistics and kidney teams, which is in good agreement with the "lettre de mission" for UMR 181. A clear synergy between biostatistics and antimicrobial resistance projects should be implemented. The departure of a key-member of the team may also be a problem in the future. It is important to note that there has been a great effort to acquire relevant skills in the team (bacteriology, molecular biology and molecular epidemiology) and that the team largely contributes to animal facilities for all the TGU.

There has been some work on biostatistics relative to "omics" analysis which was risk-taking because far from the expertise of the team, with a certain success.

The 5 scientists of the team belong to the ENVT and are concerned by teaching. They participate to university masters. One member of the team is the current president of the European College of Veterinary Pharmacology and Toxicology, one of the 21 Boards constituting the European Veterinary Specialization.



- **Appreciation on the project**

The project is composed of two sub-projects, one on biostatistics and one on antimicrobial resistance. The first one consists in a survey of “omics” developments and the continuation of previous projects on statistics and population and PK/PD modelling. The “omics” part is relevant for the TGU, but not for the team for which the field of competence is PK/PD, in particular with the departure of the only researcher with publications in “omics” data analysis. This should be better associated with “omics” platform developments and the whole team should refocus its statistical activities on PK/PD modelling. From this point of view, the choice of continuing collaboration with clinical researchers is coherent with the methodological developments in antibiotics resistance and the local influence of the team. The questions raised by the project on antimicrobial resistance are relevant. All the members of the team, including biostatisticians, should be involved in this project to make it feasible. Based on the scientific expertise in TK/TD of the team, we would also have expected more information on the future collaborations with E6, E7 and E8 teams.

There is little originality or risk-taking in the sub-project on biostatistics compared to the previous one. The sub-project on antimicrobial resistance is original with new questions, in particular in field investigations, mathematical models for bacterial population dynamics, interaction between host defense and pathogen virulence under antimicrobial treatment.

- **Conclusion**

- **Overall appreciation**

The team is locally and internationally well recognized with a good publication policy in its fields of competence. It is split in two sub-teams with few interactions in the past and in the future.

- **Strengths and opportunities**

- Local and international visibility.
- Pluridisciplinarity in the field of antimicrobial resistance
- TOXALIM platforms in support of the activities of the team.
- Links with industrial partners.
- High involvement in teaching.

- **Weaknesses and threats**

- Too much dependency on the visibility on one person.
- Lack of contribution of “generic” mathematicians to the project on antimicrobial resistance.
- Low students and post-docs attractiveness.
- Balance between private and public fundings.

- **Recommendations**

- Increased co-operation between members of the team should lead to the selection of a limited number of carefully defined aims with a high potential impact.

- Focus on PK/PD modelling with antimicrobial resistance as main research domain.
- Better incorporate generic biostatistical developments into the experimental developments.
- Search for public fundings (ANR, pesticides program).



**Team 8:** Genotoxicity signalling

**Team leader:** Mme Gladys Mirey

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	1 to be recruited
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	
N6: Number of Ph.D. students (Form 2.7 of the application file)	6+2 forthcoming	1
N7: Number of staff members with a HDR or a similar grade	$\geq 4$	2

- **Appreciation on the results**

This group is focused on basic aspects of DNA damage induction, its repair and DNA damage triggered signaling, with special emphasis on DNA double-strand break repair. The group has a strong background activity in the field. Thus, Bernard Salles' team identified the B-NHEJ pathway of repair of DNA double-strand breaks (DSBs) and demonstrated that Cernunnos, a newly identified DNA repair protein, is involved in the stabilization of the C-NHEJ (classical NHEJ) ligation complex. Today, B-NHEJ is defined as an error-prone backup repair system that requires PARP-1, XRCC1, ligase III and Cernunnos.

The scientific activity include 28 A ranked publications from 2005 to 2009 (0.7 per searcher per year) with many articles in highly ranked journals: 4 JBC, 3 Cancer Res., 1 Blood, 1 EMBO Report. Production of the different scientists is very heterogeneous.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The team has a high international visibility with 19 invited international conferences (B. Salles 13). However there is No post-doc, 1foreign PhD (Taiwan).

The ability to raise funds is significant . The team is labelled LNCC 2004-2009, and obtain 3 INCA programs, grants from canceropôles (2), EDF (2), CEA (1).

The participation to international or national scientific networks is limited: only one international collaboration (Canada) attested by a shared publication.

The team has developped good collaboration with Laboratoire Pierre Fabre; a microplate assay devoted to pharmaceutical screening is in development.

- **Appreciation on the strategy, governance and life of the research unit**

The team develop initiatives aiming at scientific coordination such as the organization of one international meeting, 3 national meetings (SFTG) and 2 workshops.



The new team MICA results from a risky project.

The Involvement of the unit's members in teaching activities is important.

It includes creation and past direction of the Ecole Doctorale "Biologie-Santé-Biotechnologies" in Toulouse, direction of a master speciality (cancerology) in Toulouse III, involvement in the national master of toxicology.

The past team leader was director of research units in IPBS (CNRS UMR5089)

then in INRA (UPR66) with participation in many national and European committees for evaluation of research (MESR, CNRS, INSERM, INRA, AERES and European Community).

- **Appreciation on the project**

The scientific project is pertinent and based on the expertise of the team in genotoxicity and DNA repair signalling. 4 programs are planned, which looks ambitious with regard to the small size of the team. However, the recruitment of another scientist (CR INRA) is expected soon which appears essential.

Among these projects, 2 might be considered as innovative projects, the first one technologic (development of new nanobodies tools in order to assay double strand breaks) while the the second one is risky (DNA repair mechanisms after colibactin exposure in intestinal cells).

- **Conclusion**

- **Overall appreciation**

The group leader is a young and promising scientist, who joined the group 1 year ago. Thus, the group can be considered as a promising start-up. The group is small and it will be a challenge for its leader to manage the group and to establish a powerful working team. The projects are clearly presented, highly innovative and worth to be supported.

- **Strengths and opportunities**

- 2 young assistant Pr recruited.
- High level of publication.
- A well defined and innovative project.

- **Weaknesses and threats**

- The split from UMR CNRS 5089 weakens the team.
- The lack of post-doc fellowship needs to be corrected.
- Integration in national and international networks looks limited.

- **Recommendations**

- Preserve collaboration with « DNA repair » team issued from UMR CNRS 5089 in order to maintain a high level of publication.
- Strengthen the team by recruiting a full-time scientist.
- The group should be encouraged to offer their skills to other groups for collaboration. We especially recommend, using the tools of determining genotoxic responses, to collaborate with project E2, E9 and E10 in determining the role of food-born genotoxins in DSB formation and repair.



**Team 9:** Promotion and prevention of colon carcinogenesis by food constituents

**Team leader:** M. Denis CORPET

- Staff members (see the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	1
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation of the results

The main research objective of this team is to answer the question why consumption of red meat and processed meat is associated with elevated colon-cancer risk, and how this can be prevented. The focus is on verifying the hypothesis that haem iron in red meat enhances lipid peroxidation in the digestive tract, which generates mutagenic toxic aldehydes that are also cytotoxic. The team wishes to verify in their future work the quite attractive hypothesis that genotoxic species formed in the gut as a result of haem intake may selectively kill normal cells, which may lead to expansion of premalignant *APC*-mutated colon cells. The team uses animal models of digestive cancer (liver, colon), pre-neoplastic markers (aberrant crypt foci, mucin-depleted foci) and cell lines that are mutated in the *APC* gene. To prevent the tumour-promoting effect of consumption of red meat, calcium and antioxidants are used in the experimental settings.

Several possible explanations are given for the cancer-promoting effects of meat intake: (i) high fat or high meat in the diet could act as a promoting factor in colon carcinogenesis, (ii) high-temperature frying or cooking of meat causes formation of mutagens, which may initiate colon carcinogenesis, (iii) endogenous nitrosation causes formation of nitroso-compounds in the stomach, (iv) haem iron generates oxidative stress *via* lipid peroxidation. The group focuses on the last-mentioned hypothesis, which seems to be quite attractive and novel.

The Committee noted that only the fourth explanation is specific for red meat. The food mutagens mentioned in (ii) also occur in fried fish and other foods, and endogenous nitrosation (iii) is a result of the presence of nitrate/nitrite in processed meat. In the text and in the oral presentation by the team leader these different aspects were somewhat mixed-up and not clearly distinguished.

The scientific output of the team is good, although heavily dominated by the two senior scientists. The team leader has published approximately 60 papers overall (1983-2008), half of which as first author. His senior co-worker has published 21 papers (7 as first author). Of the 36 papers published by the team in the period 2005-2009, 10 appeared in Journals with an impact factor > 4. In this period, the two senior scientists received 13 invitations to give lectures during international meetings; on 17 occasions, members of the team gave oral presentations or presented posters. Four theses were completed during this time period.



- **Appreciation of the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The research of this team is rather unique, as the activities of two competing groups (The Netherlands, USA) will soon cease. The focus of the work is on red meat and processed meat. If the effect of processed meat is maintained as one of the research objectives, this should be given more attention, e.g. by investigating intake of meat processed with nitrite/nitrate, conditions of endogenous nitrosation in the stomach, effects of vitamin C and other anti-oxidants to mitigate nitrosation, etc. If the team chooses to remain focused on the tumour-promoting effects of red meat, the research should be extended to mechanistic studies of the underlying process: haem iron-mediated lipid peroxidation, formation of aldehydes like 4-hydroxynonenal, DNA-adduct formation by these aldehydes in critical genes, mutation induction, etc. Collaboration on these aspects, with other teams in Toxalim and with research groups elsewhere, is strongly recommended.

Collaborations exist with scientists in France (Nantes; Paris), The Netherlands (Wageningen), the United Kingdom (University of Cambridge), Croatia (Zagreb), Canada (University of Toronto), USA (University of Omaha) and Mexico (CRAS).

There is no mention of prizes and distinctions. In the period 2005-2009 the two senior scientists received 13 invitations to give lectures during international meetings (team leader, 7; senior scientist, 5; junior scientist, 1). On 17 occasions members of the team gave oral presentations or presented posters.

The team is coordinating 1 ANR project (HemeCancer, PNRA-2005-2009), and is a partner in another one with ToxAlim team E4 (Colbactin, Emergence-2007-2010).

- **Appreciation on the strategy, governance and life of the research unit**

The 2 senior scientists are heavily involved in teaching and training, both spending >190 hours per year on this activity. Another member of the team teaches undergraduate students (oncology, 3 hours per week during three weeks).

- **Appreciation of the project**

- **Strengths :**

The research is focused on a highly relevant topic in food toxicology.

The research utilizes relevant animal models and modern techniques and analytical methods.

The work of the team leader is widely known and recognized.

The team works enthusiastically on their colon-cancer model.

- **Weaknesses :**

The research is focused on only one topic in food toxicology (red meat/cancer).

The international collaboration of the team is rather limited.

The research program is weak with respect to mechanistic studies.

The research plan of the two recently recruited co-workers is unclear.

- **Opportunities :**

Intensification of collaboration with other teams in Toxalim and at the international level should be possible, certainly on molecular mechanistic aspects such as DNA-damage induction by 4-hydroxynonenal and subsequent DNA repair, mutation induction, signalling and mechanisms of cell death in the colon.

- **Threats :**

The unique research niche may lead to isolation of the team within Toxalim.





## – Recommendations :

Collaboration with other ToxAlim groups is highly recommended. This should also help evaluate other mechanisms of red meat toxicity.

Strengthen mechanistic aspects of the projects.

Clearly define the subprojects of the scientists who joined the unit recently.

**Team 10 :** Toxicologie cellulaire, moléculaire des xenobiotiques

**Team leaders:** M. Roger RAHMANI and Mme Laurence GAMET-PAYRASTRE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This team was created in 2008 by the fusion of the Cellular, Molecular and Genomic Toxicology Group (TCMG, Sophia Antipolis INRA Institute) with part of the BIOTTOX Group, UMR 1089, Toulouse. The TCMG group (headed by R. Rahmani) was in the INRA 1112 Unit (Sophia Antipolis) from 2000 to 2007 and only recently joined the Xenobiotics Unit in Toulouse. This fusion was driven by the long established collaborations with the INRA Unit 1089 and the general INRA policy of federating forces in Chemical Food Toxicology and Safety. The UMR 1089 part included 3 full-time CR INRA and 2 technicians. Since the researchers have not been working together during the 4 years studies on different subjects are logical. Obviously the quality of these studies, mainly on the antitumoral effects of food contaminants and toxicity of pesticides is variable and the team is too small to have sufficient expertise in all the technologies it is using.

Altogether the present members of the team have produced 24 publications plus a paper in Biofutur and a book chapter. They have also produced 18 scientific communications (7 were oral communications) and one patent. They have made 11 invited conferences (only one abroad, in a pharmaceutical firm in Basel) and supervised 6 theses. Overall, this scientific production appears to be satisfactory; however, the highest IF of the publications remained around 5 and the scientific production of the different members was not equal.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

The team has not been awarded any price and has not received any invitation to international conference or symposium. One invitation abroad in an institute. Several invitations in France.



The team has recruited one post-doc (previously a PhD student in the lab). It is attractive for PhD students (6 theses during the past 4 years).

The team has successfully applied for funds during the past years; i.e. through its participation in ANR projects and has fruitful collaborations with other french teams. Moreover, since a number of years R.Rahmani has established strong and productive collaborations with surgeons of the Nice hospital and the Galderma firm (CIFRE contracts,...).

The team is involved in national networks (3 ANR) but does not participate in international networks and has no collaboration with a foreign partner.

- **Appreciation on the strategy, governance and life of the research unit**

The team is working in two different sites; the group working in Sophia cannot move to Toulouse for personal and scientific reasons. Nevertheless, its governance was well explained during the committee visit: R. Rahmani (Sophia) is the leader and another researcher will act as a local co-leader. They will interact through regular meetings and video-conferences. The group located in Sophia takes benefit of its strong link with the Nice hospital (availability of human liver samples and scientific collaborations); the access to a transcriptomic platform and long-term collaborations with the cosmetic firm Galderma.

The group has been able to propose a more focused and sound project with the 4 permanent researchers working together.

The team is composed of only full-term researchers and consequently has no teaching duties. Its members are involved only in some specialized courses.

- **Appreciation on the project**

The project is centered on the short-term and long-term effects of low doses of individual and combined food contaminants on human physiology and health risks. It is divided in 3 parts that are strongly linked. (i) The effects of maternal chronic exposure to pesticides on mouse offspring and mother by investigating alterations occurring on haematopoiesis, immunity, liver and neural system. (2) The effects of current dietary pesticides on gene deregulation in human liver parenchymal cells with the objective to identify biomarkers and mechanisms involved.(iii) the role of adipose tissue in mediating the effects of contaminants on the regulation of selected physiological functions. All these subjects are timely and important scientific and health questions.

Although these subjects are highly competitive at the national and international levels, the team has a good expertise and should be able to bring original contributions during the next 4 years.

The group is participating in several national projects and the leaders have demonstrated they are able to raise financial supports.

Overall this project appears sound and ambitious. Efforts have been made to focus the global project. Nevertheless it is still quite large for the size of the team and requires various expertises that cannot be all gathered by the members. Strong collaborations with other teams of the TGU are highly encouraged.

- **Conclusion**

- **Overall appreciation**

This recently created team has made a lot of efforts to design an interesting and focused project that fits well in the priorities of the TGU and it can be considered as an important player in the scientific performance of the TGU during the next 4 years.

- **Strengths and opportunities**

An interesting project that includes investigations on long term effects of low doses of pesticide mixtures.

Unique expertise in some cell models which will be also very useful for other teams of the TGU (especially human hepatocyte cultures).



Good expertise in various cellular and molecular technologies.

The team is engaged in national networks supported by ANR.

Attractive for PhD students.

– Weaknesses and threats

This a small group; only one full-time researcher based in Sophia (the head of the team).

Among the technologies that will be employed, microarrays will occupy a predominant place. The team must be aware of the limitations of this technology emphasized by others (e.g. Toxcast project in which toxicity screening using microarrays appears more and more disappointing); the team should take more into consideration other “omic” technologies (including metabolomics) and other approaches.

Publications are in journals of IF 5 or lower.

– Recommendations

The project of team 10 is in the heart of the TGU objectives and collaborations with other teams of the TGU, as announced in the oral presentation, are highly encouraged.

Collaborations with foreign teams is also encouraged.

The team should be encouraged to publish some of their results in journals of higher IF.

More full-time researchers in the Sophia site would be helpful.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	A	A+	A

Team 1: Integrative Toxicology and metabolism

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A



### Team 2: Metabolism of Xenobiotics

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

### Team 3: Endocrine Disrupting Pesticides

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	non noté	B

### Team 4: Neuro-Gastroenterology and nutrition

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	non noté	A

### Team 5: Immunomycotoxicology

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A



Team 6: Membrane transporters and resistance

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	non noté	B

Team 7: Pharmacokinetics Pharmacodynamics and Modelisation

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	A	non noté	B

Team 8: Genotoxicity signalling

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	non noté	A

Team 9: Promotion and prevention of colon carcinogenesis by food constituents

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	A	non noté	B



Team 10: Toxicologie cellulaire, moléculaire des xenobiotiques

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	A	non noté	A

*Pr. Bernard Salles*  
*Directeur*

Toulouse, July 2nd, 2010

To Robert Barouki, President of the visiting committee and Pierre Bedossa, the AERES Delegate

I would like to thank the members of the visiting committee for the quality of the evaluation that allows us to take into account most of the suggestions raised. Despite the fact that specialized research cannot be published in the high impact reviews as project in human medicine and molecular genetic, the evaluation was fairly conducted. However, the comparison between INSERM or CNRS teams and INRA teams should take into account the specificity of the research in agro-veterinary field we currently develop in the unit. Despite this specific criticism, we collectively share the evaluation.