Market approval of the phytosanitary active substances in Europe: a theoretical and empirical duration analysis*

Joel Aka†

September 2013

Abstract

We analyze the main determinants of the examination delays of plant protection active substances in Europe. One interesting feature of this review process is that it is based both on a decentralized examination by rapporteur country and on a centralized examination by the European Food and Safety Authority (EFSA). We build a simple model of the European review process of the plant protection active substances. Among the predictions, the model shows that the high quality products are reviewed faster than the low quality products if the firms expect higher profit payoffs for high quality products.

This prediction is in line with the evidence we obtain from the pesticide database of the EFSA. We also find that, the insecticides obtain a market approval much faster than herbicides. Active substances with significant risk of cancer, toxicity and genotoxicity are approved less quickly than those which are less risky. The ecotoxic products are approved faster at the national level but slowly at the EU level. About the geographical zone of the rapporteur country, the center zone review faster. Finally, the products of the European firms are approved more quickly than the products of the foreign firms. A log-logistic survival model is the preferred parametric specification, and the results suggest that the hazard function is nonmonotonic over time.

Key words: Duration model, standard survival analysis, competing risks models, examinations delays; centralized review, decentralized review.

*I would like to thank Stéphane Lemarié, Iragael Joly, Katharine Rockett, for help they have given me for this work.
†PhD student in Economics, UMR GAEL-INRA (France)

1 Introduction

The marketing of a new plant protection product is subject to a previous approval. The approval procedure[1] is to ensure that these products do not have unacceptable toxic effects on human health and the environment and to establish conditions under which these products are deemed efficient. The administrative procedure of the approval provides a delay that can range from 20 months and 15 days to 32 months and 5 days[2]. However, the delays that we observe with our data vary from 38 months to 215 months, which is much greater than the delays described in the administrative regulatory procedure.

That is why, the purpose of this paper is to analyse empirically the main determinants of the examination delays of active substances in Europe. Indeed, grant a market approval or not may depend on the inherent factors that affect the review process, such as risks and benefits of pesticide use, biological activity, the role of regulatory factors and the characteristics of the plant protection firms. The examination delay here, measures the time elapsed between submission to a regulatory agency and the market approval and contrary to Dranove and Meltzer (1994)[3] , it does not take into account the time elapsed between the discovery of the molecule and the date of submission for market approval.

In the empirical literature, this review time is used as a measure of the regulatory stringency. For instance, in previous studies of US Environmental Protection Agency regulation,Upton (1982) and CAST (1981)[4] used the time required from pesticide discovery to EPA registration (development time) as a measure of the regulatory stringency. The basic intuition is that, the review time becomes longer when regulation becomes more stringent. Since registration time depends on the number of tests that regulators must examine, an increase on this number will increase the registration time. In Europe, the European Commission Regulation (2009) concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, provides more complex tests.

Thus, analyse empirically the main determinants of delays of market approval of phytosanitary active substances may be similar to an empirical analysis of the main determinants of regulatory stringency. This is very important because market approval process of plant protection products, may be seen as an entry barrier (Dean et al., 2000; Helland and Matsuno, 2003; Klapper et al., 2006; Prantl, 2012). This entry barrier or entry regulation may have both a positive and a negative impact on innovation. Indeed, market entry regulation increases the hurdles for companies to enter a specific market. This may be positive for the incumbents, because it reduces the competitive pressure and allows them to invest more resources in risky innovation activities assuming a rather high level of competition intensity (Dean et al., 2000; Helland and Matsuno, 2003; Klapper et al., 2006; Aghion et al., 2009; Prantl, 2012). However, market entry barriers make it very difficult for innovative companies to enter a market, which is negative for the overall innovative performance in these markets, especially if the competition intensity is

[1] In Europe, these procedures are investigated by European authorities or by mutual recognition within a zone. In particular, active ingredients are approved at European level and the pesticides formulation at national level, with mutual recognition (the European Commission Regulation (2009)).

[2] See the European Commission Regulation (2009)

[3] Dranove and Meltzer (1994) measure the time to approval by the time elapsed between the discovery of a new drug and the date where this drug gets market approval. They use the date of the submission of the product to a patent office as the discovery date. However, they do not fail to point out on the one hand, the difficulties in identifying the dates of the submission of the product to a patent office and, on the other hand the unavailability of these dates for several new molecules.

[4] The Council for Agricultural Science and Technology (CAST)

still rather low (Dean et al., 2000; Helland and Matsuno, 2003; Klapper et al., 2006; Aghion et al., 2009; Prantl, 2012).

Otherwise, some empirical papers on the examination delay shows that the review time may be affected by the characteristics of both the applications and the applicants. About the link between the review time and the characteristics of the products,Dranove and Meltzer (1994) shows that drugs of great importance are approved faster than those that are less important. Similarly, Harhoff and Wagner (2009) and Regibeau and Rockett (2010) more important innovations are approved more quickly. Other studies analyse the determinants of the rate at which drugs are reviewed by the FDA according to the characteristics of firms that submit their products. In particular,Olson (1997) shows that the regulator respond to firm-specific characteristics when evaluating new drug applications. These characteristics are perceived by the regulator as a signal of the quality of the drug and the reputation of the firm. For example, firms that invest more in R&D or which are specialized only in the production of drugs, have their products reviewed faster than others. Also, the products of firms which submit more than one drug to the FDA are revewed faster. Finally, drugs of foreign firms are reviewed faster than drugs of local firms. In a recent paper, Xie and Giles (2011) analyses the length of time that it takes for a patent application to be approved by the U.S. PTO, conditional on the patent actually being awarded eventually. They show that, the number of claims, the number of citations, the patent's technological category and the type of applicant have significant effects on the duration of patent approval. In the field of pesticides regulation, Cropper et al. (1992) investigate the determinants of U.S. EPA decision making on pesticide regulation. They find that risks to the environment and health increased the probability that the pesticide was forbidden. At the same time, larger benefits associated with the use of a pesticide and comments by grower associations on the need for it reduced this probability.

The results of these papers are interesting but they take account only one type of event except Harhoff and Wagner (2009). The review of an innovative product, as a matter of fact, may lead to the approval, the rejection or the withdrawal of the product. But, the articles mentioned above take into account only approved products for reasons related to some difficulties to find data on rejected products. Harhoff and Wagner (2009) in their analysis of review times for innovative products, correct this selection bias by using competing risks models. The expression competing risks is relative the field of survival analysis, where subjects under investigation are exposed to more than one possible type of events. Therefore, in this paper we use both standard survival analysis competing risks models. One interesting feature of this regulation is that it is based both on a decentralized examination by rapporteur country and on a centralized examination by the European food safety authority (EFSA). We find that, the insecticides obtain a market approval much faster than herbicides. Active substances with significant risk of cancer, toxicity and genotoxicity are approved less quickly than those which are less risky. The ecotoxic products are approved faster at the national level but slowly at the EU level. The new active substances obtain a market approval much faster than existing products for the entire process but for the national procedure, existing active substances are reviewed faster. About the geographical zone of the rapporteur country, the center zone review faster. Finally, the products of the European firms are approved more quickly than the products of the foreign firms. The rest of the paper is organised as follows: in Section 2, we describe the European market approval procedure of phytosanitary active substances. In Section 3, models on standard survival analysis and competing risks are reviewed. In Section 4 we present the main results and the Section 5 conclude the paper.

2 The description of the approval process of active substances

The active substances approved by the Standing Committee on Plant Health are registrated on the positive list of active substances (which forms 'Annex I' of the European Commission Directive (1991)) that have been shown to be without unacceptable risk to people or the environment. The approval procedure active substances either as existing active substances or new active substances, is described as follow:

- **Step 1: The national admissibility of the application**

The active substances are approved at European level but reviewed at national level. In doing so, an application for the approval of an active substance shall be submitted by the producer of the active substance to a Member State or the rapporteur Member State, with a complete dossier. This rapporteur Member State has 45 days from receipt of the application for the approval to make its national report admissibility. If one or more elements of the application are missing, the rapporteur Member State shall inform the applicant, setting a period of a maximum of 3 months for their submission.

- **Step 2: The Draft assessment report**

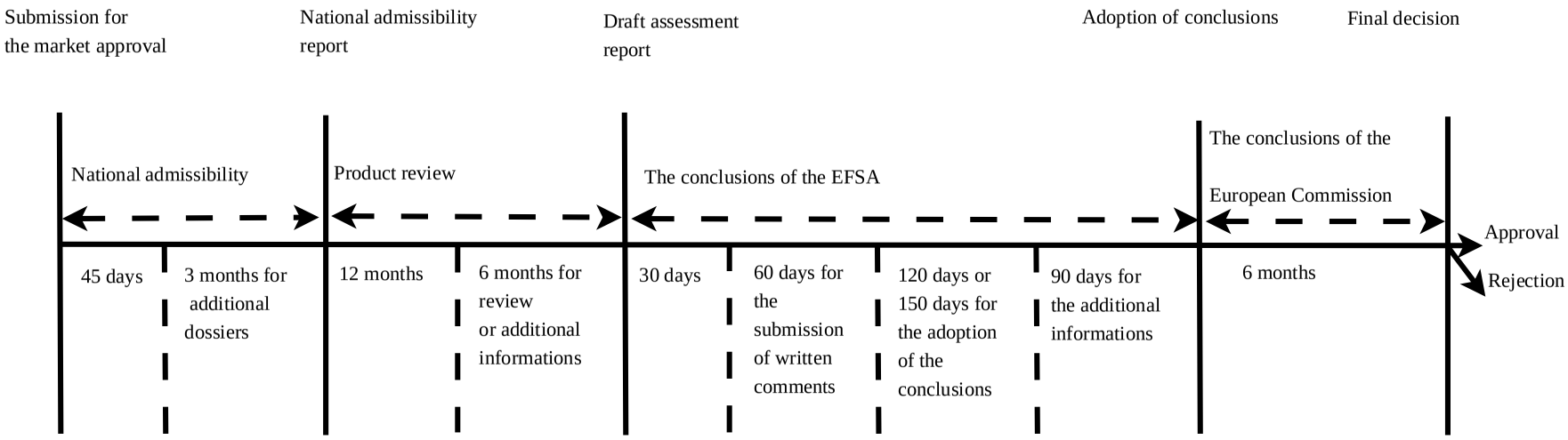
The rapporteur Member State, within 12 months from the date of the national admissibility of the application, shall prepare and submit to the Commission, a report, referred to as the 'draft assessment report', assessing whether the active substance can be expected to meet the approval criteria.

- **Step 3: The European Food Safety Authority (EFSA) conclusion**

The EFSA shall circulate the draft assessment report received from the rapporteur Member State to the applicant and the other Member States at the latest 30 days after its receipt. Also, the EFSA shall allow a period of 60 days for the submission of written comments and within120 days of the end of the period provided for the submission of written comments; it shall adopt its conclusion. In the event of a consultation, the 120-day period shall be extended by 30 days. Finally, if the EFSA needs additional information; it shall set a period of a maximum of 90 days for the applicant to supply it to the Member States, the Commission and the EFSA.

- **Step 4: European Commission decision**

Within six months of receiving the conclusion from the EFSA, the Commission shall present a report, referred to as 'the review report', and a draft Regulation to the Committee, taking into account the draft assessment report by the rapporteur Member State and the conclusion of the EFSA. If the approval requires confirmatory information, the rapporteur Member State shall assess the additional information and submit its assessment to the other Member States, the Commission and the EFSA without delay and at the latest six months after the receipt of the additional information. Finally, Commission decides whether to include the active substance in Annex I of the European Commission Directive (1991) for a period of 10 years renewable (see schema on page 5 which summarises the main steps of the administrative approval procedure).



Minimum examination delays: 20 months and 15 days; Maximum examination delays: 32 months and 5 days

Figure 1: Administrative approval process

Along this standard approval procedure, there is an accelerated procedure[5]. This procedure may be required by the applicant under certain conditions. In particular, according to the European Commission Regulation (2008), this process may be required by the applicant provided that there is already a draft assessment report for its product and an application of market approval is submitted within an acceptable time following a non-listing decision in Annex I.

3 Theoretical analysis

3.1 A simple model

In this section, we model the approval process of the plant innovation that might help interpret some of the econometrics results we obtain in the empirical analysis. We have the same assumptions as Regibeau and Rockett (2010) but with some changes. These changes are based on some specific features of the certification process of the plant protection products. That being said, the central idea in their paper is that the delay depends on the interaction between the certifier and the applicant. The applicant make an effort that can reduce the approval delays.

We consider three units of this certification: a single firm and a publicly-run certifier in the country $k = (A, B)$[6]. In order to focus our attention on the examination delays, we don't consider any strategic interactions between countries A and B. Also, the single firm can seek approval for its patented product from the certifier. This certifier may then approve or reject the product, based on the results of the review process. A product is approved if some threshold evaluation of quality by the certifier is passed. Especially, there are two types of plant protection products, l (low quality product) and h (high quality product). For the low quality products, the health and environmental consequences are worse in expectation compared to the expected benefits, while the high quality products meet the criteria of quality, efficiency and safety. The exogenous proportion of high quality products are defined as λ.

We assume that the firm knows the level of quality of its product for sure, but the certifier does not. Determining the type of the plant protection product is precisely the purpose of the certification process. Unfortunately, this certification process is imprecise. In each country, then, the inspection generates a signal of the product's true value, where the probability that the signal is "correct" is, p_k . In other words, p_k is both the probability that a high quality product is approved and the probability that a low quality product is rejected. Similarly, $1 - p_k$ is the probability of an "incorrect decision". Notice that these are conditional probabilities i.e. p_k is the probability that a product is judged high quality given that it truly is high quality or the probability that a product is judged low quality given that it truly is low quality. Note that, contrary to Regibeau and Rockett (2010), the probability p_k in our model does not depend of the innovation cycles and learning but we assume that it can differ across countries with $p_A > p_B$ and $p_k > 1/2$.

The product generates a certain value if it is introduced in the market. That being said, the private value of a

[5]In our data, we have 62 active substances concerned by this procedure with a review time which varies between from 15 to 38 months. We don't take into account in our analysis the products concerned by the accelerated process.

[6]Note that, in Europe, the certification process for active ingredients is a centralized process, but the scientific review of the product is made by a country called rapporteur country. This rapporteur country writes a review report including a recommendation about the inclusion or not in Annex I. That's why, in our model we consider two countries.

high quality product to the firm when it is approved, are flow profits ν_h for the length of the market approval L. The private value of a low quality product that is mistakenly approved makes it possible for the firm to earn positive flow profits of ν_l. If both high quality and low quality products are rejected the private value is zero and we assume that $\nu_h > \nu_l$. In Regibeau and Rockett (2010), if a good application is not approved, the innovator can still exploit the innovation as a trade secret and obtain total discounted private benefits. It is not the case in our model, even if we can assume that a rejected product may be sold illegally.[7] So, in our model there is no private benefits for a high quality product when it is rejected and when its review is pending.We also assume that both 'high quality' and 'low quality' applications can be more or less 'important' and the parameter α_j with $j \in (1,2)$ is a measure of the importance of the active substance. Precisely, α_j denotes the plant protection product of importance j with $\alpha_1 > \alpha_2$. There is a proportion γ of α_1 plant protection product. This proportion is the same for high or low quality product.

Firm can exert effort to make its product comply with the standards of approval and the time d that elapses the time between the submission of product to certifier and the date at which the market approval is either granted or denied, depends on the effort exerted by the applicant. Remember that, we assumed that firm knows the level of quality of its product for sure, and then knows the potential importance of its product. In other words, firm knows α_1 or α_2 . In doing so, we can distinguish between four levels of effort. In particular, we define e_{ij} as the effort of a type i applicant with an active substance of importance j:

$$d = d(e_{ij})$$

With $i \in (1,2)$, $j \in (1,2)$, $d' < 0$, $d'' > 0$ and $\lim_{e \to \infty} d \geq 0$. Exerting effort is costly and we define the cost of exerting effort as $c(e_{ij}) = e_{ij}$.

4 Equilibrium and main properties

The firm´ s expected payoff value of a high quality plant protection product from a single country´ s certification process is:

$$E(\nu)_{hj} = p_k \int_{d(e_{hj})}^{d(e_{hj})+L} \alpha_j \nu_h exp(-rt)dt - e_{hj}$$

This expected profit can be rewritten as:

$$E(\nu)_{hj} = \frac{\alpha_j \nu_h p_k}{r}(1 - exp(-rL))exp(-rd(e_{hj})) - e_{hj}$$

The optimal level of effort is obtained by maximizing $E(\nu)_{hj}$ with respect to e_{hj}:

$$-\alpha_j \nu_h p_k (1 - exp(-rL))d'(e_{hj})exp(-rd(e_{hj})) - 1 = 0$$

[7] The European Crop Protection Association (ECPA) in its 2008 report, estimates that 5% - 7% of annual turnover is affected by counterfeiting and illegal trade. This is about €360 - €510 million of the European pesticide business across Europe.

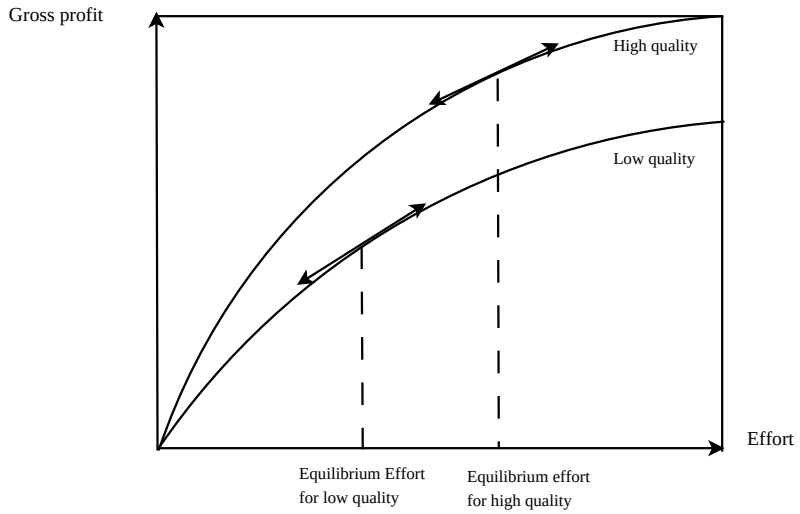


Figure 2: Equilibrium efforts

Similarly, the firm´ s expected payoff value of a low quality plant protection product from a single country´ s regulatory process is:

$$E(\nu)_{lj} = (1 - p_k) \int_{d(e_{lj})}^{d(e_{lj}+L} \alpha_j \nu_l exp(-rt)dt - e_{lj}$$

The above expression can be written as:

$$E(\nu)_{lj} = \frac{\alpha_j \nu_l (1 - p_k)}{r}(1 - exp(-rL))exp(-rd(e_{lj})) - e_{lj}$$

The optimal level of effort is obtained by maximizing $E(\nu)_{lj}$ with respect to e_{lj}:

$$-\alpha_j \nu_l (1 - p_k)(1 - exp(-rL))d'(e_{lj})exp(-rd(e_{lj})) - 1 = 0$$

Using these two derivatives, we get the following proposition:

Proposition 1. *Firms exert higher effort for high quality products than for low quality product if they expect higher profit payoffs for high quality product (see figure 2). So, the high quality products are reviewed faster than the low quality products.*

Proof. we can show that, for a given value of e_{lj}, $\frac{\partial E(\nu)_{hj}}{\partial e_{hj}} > \partial \frac{\partial E(\nu)_{lj}}{\partial e_{lj}}$ if and only if $\frac{\nu_h}{\nu_l} > \frac{1-p_k}{p_k}$ (1). So, this condition is verified because $p_k > 1/2$. Indeed, if $p_k > 1/2$, then $\frac{1-p_k}{p_k} < 1$. Since $\frac{\nu_h}{\nu_l} > 1$ then $\frac{\nu_h}{\nu_l} > \frac{1-p_k}{p_k}$ (1) and $e^*_{hj} > e^*_{lj}$. □

Now, we turn focus our attention on two effects of the equilibrium. The first configuration is the link between the equilibrium examination delays,d , and the importance of the applications and the second is the relation between the examination delays and the accuracy of the review process. Furthermore, from the two first order conditions derived above, and assuming that the second order conditions are satisfied everywhere i.e. $S.O.C < 0$, we get:

$$\frac{de_{hj}}{d\alpha_j} = \frac{\nu_h p_k (1 - exp(-rL))d'(e_{hj})exp(-rd(e_{hj}))}{S.O.C} > 0 \quad (1)$$

$$\frac{de_{lj}}{d\alpha_j} = \frac{\nu_l(1-p_k)(1-exp(-rL))d'(e_{lj})exp(-rd(e_{lj}))}{S.O.C} > 0 \tag{2}$$

The derivatives 1 and 2 above are positives everywhere leading to our second proposition.

Proposition 2. *The effort is higher for more important products, regardless of type i.e.* $e^*_{i1} > e^*_{i2}\ \forall\ i \in \{l,h\}$ *(see figure 3). Thus, more important products are approved (or rejected) faster than less important products.*

As explained by Regibeau and Rockett (2010), the benefit of exerting effort is to bring forward the expected payoff from receiving an approval. This benefit is higher for a product with a high importance.

Our second aspect of the equilibrium is the link between the examination delays and the accuracy of the review process. Using the two first order condition and assuming that the second order conditions are satisfied everywhere i.e. $S.O.C < 0$, we obtain:

$$\frac{de_{hj}}{dp_k} = \frac{\alpha_j\nu_h(1-exp(-rL))d'(e_{hj})exp(-rd(e_{hj}))}{S.O.C} > 0 \tag{3}$$

$$\frac{de_{lj}}{dp_k} = -\frac{\alpha_j\nu_l(1-exp(-rL))d'(e_{lj})exp(-rd(e_{lj}))}{S.O.C} < 0 \tag{4}$$

We note that the derivative 3 is positive everywhere but the derivative 4 is always negative. From these two effects, we get the following proposition:

Proposition 3. *The equilibrium effort for the high quality products increases as the precision of the review increases i.e.* $e^*_{hjA} > e^*_{hjB}$ *. For the low quality products, the equilibrium effort decreases as the precision of the review increases i.e.* $e^*_{hjA} < e^*_{hjB}$*. So, the examination delays are for longer the low quality products and shorter for the high quality products.*

With $p_k > 1/2$ (i.e., the review process improves on a random one), the gap between the equilibrium effort for the good products and the equilibrium effort for the bad products is larger. These two equilibrium efforts diverge strongly. In this case, the examination delays are longer the bad products and shorter for the good products. When we consider two countries A and B with $p_A > p_B$, the divergence is stronger in the country with the higher p_k .

Graphically, we have:

5 Empirical model

The above description of the European market approval procedure phytosanitary active substances is important. It may help to understand if the underlying process of market approval occurs in continuous or discrete time. That being said, this administrative process of market approval is intrinsically continuous because approval can occur on any day after that the product become at risk. In other words, approvals are not made only once a month, say. Also, the literature on both the time to grant a patent (Harhoff and Wagner, 2009; Regibeau and Rockett, 2010; Xie and Giles, 2011) and the time to approve a new drug (Olson, 1997; Dranove and Meltzer, 1994) which has some affinity to our setup, used a continuous time framework.

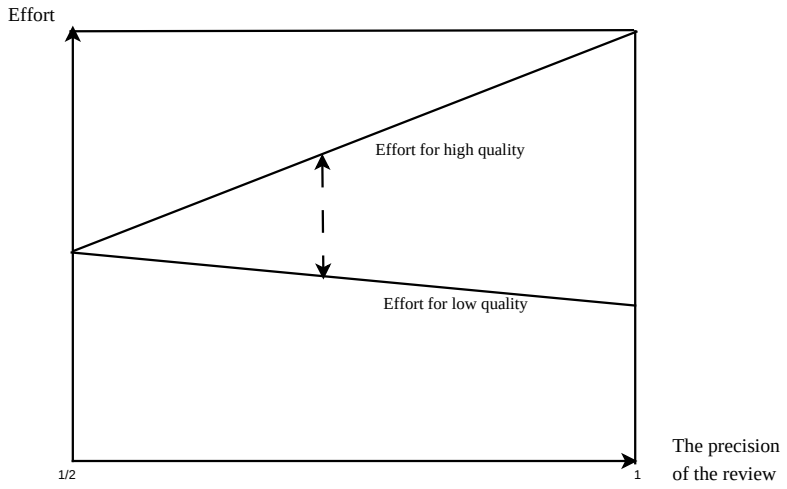


Figure 3: Equilibrium efforts

5.1 Standard single event time model

We use the terminology of survival analysis, referring to the event of interest as "market approval" and to the waiting time as "survival time". Let T be a non-negative random variable representing the waiting time until the occurrence of an event. We will assume that T is a continuous random variable with probability density function $f(t)$ and cumulative distribution function $F(t) = P(T \leq t)$ giving the probability that the event has occurred by duration t. It will often be convenient to work with the complement of the cumulative distribution function, the survival function which gives the probability of being alive at duration t, or more generally, the probability that the event of interest has not occurred by duration t. It will often be convenient to work with the complement of the cumulative distribution function, the survival function $s(t) = 1 - F(t) = P(T \geq t)$ which gives the probability of being alive at duration t, or more generally, the probability that the event of interest has not occurred by duration t.

An alternative characterization of the distribution of T is given by the hazard function, or instantaneous rate of occurrence of the event, defined as

$$\lambda(t) = \lim_{X\Delta t \to 0} \frac{P(t \leq T < t + X\Delta t \mid T \geq t)}{X\Delta t} = \frac{f(t)}{s(t)} = -\frac{s'(t)}{s(t)} = -\frac{d}{dt} ln(s(t))$$

The numerator of this expression is the conditional probability that the event will occur in the interval $[t, t+X\Delta t]$ given that it has not occurred before, and the denominator is the width of the interval. The integral of this hazard function is called the cumulative hazard (or cumulative risk) and is denoted

$$X\Lambda(t) = \int_0^t X\lambda(u)du = -ln(s(t))$$

We can obtain a formula for the probability of surviving to duration t as a function of either the hazard or the cumulative hazard

$$s(t) = exp(-X\Lambda(t)) = exp(-\int_0^t X\lambda(u)du)$$

and deduced that:

$$f(t) = X\lambda(t)exp(-\int_0^t X\lambda(u)du)$$

5.2 Model on cause-specific hazards

The expression competing risks in survival analysis is used to refer to a situation where subjects under investigation are exposed to more than one possible type of events. In other words, competing risks is considering with the joint distribution of failure time T and type or cause of failure D, two observable random variables. Basic quantity that derives from this approach is the cause-specific hazard function:

$$\lambda_k(t) = \lim_{X\Delta t \to 0} \frac{P(t \leq T < t + X\Delta t, D = k \mid T \geq t)}{X\Delta t}$$

with $D = 1, ..., K$.

Cause-specific hazard for a cause D is the instantaneous failure rate from this cause in the presence of all other possible causes of failure. Among the regression models for Cause-specific hazard, the Cox proportional hazards models (1972) establish a link between the cause-specific hazard and a vector of covariates x by the relation:

$$\lambda_k(t, x) = \lambda_{0k}(t)exp(X\beta x)$$

The total hazard, $\lambda(t, x)$, equals the value of its corresponding hazards function summed up to time t is:

$$\lambda(t, x) = \sum_{k=1}^{K} X\lambda_k(t)$$

This equation means that the all-cause hazard rate is the sum of K hazards. The probability of failure from cause k until time t in the presence of all other possible causes is known as cause-specific cumulative incidence and depends on the cause-specific hazards for all other causes

$$\Lambda_k(t, x) = \Lambda_{0k}(t)exp(X\beta x)$$

where

$$\Lambda_{0k}(t) = \int_0^t X\lambda_{0k}(u)du)$$

Then, we can estimate

$$s_k(t, x) = exp(-X\lambda_k(t, x))$$

from the cause-k specific cumulative hazard where $s_k(t, x)$ is the survival probability for the k^{th} risk if all other risks were hypothetically removed.

5.3 Model on a subdistribution hazards

Fine and Gray (1999) considered a regression model on the subdistribution hazard of the form

$$\lambda_k^*(t,x) = \lambda_{0k}^*(t)exp(X\beta x)$$

We can think of this hazard as that which generates failure events of interest while keeping subjects who experience competing events "at risk". For any event type, this approach focuses on the hazard associated with the cumulative incidence function (CIF), $I_k(t,x)$, which expresses the effect of covariates directly on the CIF.

The CIF on the subdistribution is the function such that:

$$I_k(t,x) = 1 - exp(-\int_0^t X\lambda_k^*(u,x)du)$$

In contrast to the cause-specific hazard that eliminates individuals who have the competing cause, subdistribution hazards include both individuals without any event and those who have had the competing event.

6 Data and assumptions

We use data which come from the pesticide properties database (PPDB) and the EU pesticides database. The data from both databases were matched in order to take into account a large number of covariates that may affect the delays of market approval of phytosanitary active substances. Our Interest is firstly focused on the survival time of the review of active substances approved by the European Commission, and secondly on the same survival time but with the inclusion of a competing event. This competing event is the rejection of the active substance. Thus, 339 active substances were matched with 272 approved, 52 rejected and 15 withdraw. Note that, more than 750 existing active substances were excluded from Annex I with only 67 products that have been re-evaluated. The others have never been re-evaluated because applicant has not submitted a complete dossier at time to the rapporteur country. All these products were observed on about twenty years from 1993 to 2013.

6.1 The dependent variable

Table 1 shows some descriptive statistics. The variable *Delay* denote the time elapsed between submission to a regulatory agency and the market approval. Unlike Upton (1982) and Dranove and Meltzer (1994), this measure of examination delay don't take into account the time elapsed between the discovery and the grant of patent. That being said, the mean of the examination delay is about 77 months for approved active substances, 68 months for rejected products and 118 months for withdraw products (see Table 1). Also, we divide the review process into national and European phases. The national phase is relative to the examination of the active substance made by the rapporteur member state which writes a review report including a recommendation about the inclusion or not in Annex I.

The European phase is about the review conducted both by the European Food Safety Authority and the European commission and which leads to a final decision. In doing so, to take into account these two phases,

Table 1: **Descriptive statistics of the examination delays by type of event**

decision	mean	sd	min	max	N
Approved	78.18846	31.13861	38	215	260
Not Approved	68.88462	32.44945	21	140	52
Withdraw	118.6667	38.10824	41	211	15
Total	78.56575	32.96188	21	215	327

we introduce two other time variables. The first variable is *Ndelay* which denote the time elapsed between the submission to a regulatory agency and date where this regulatory agency sends a review report to the European Food Safety Authority. The second variable is *Edelay* which denote time elapsed between the receipt of the review report by the EFSA and the date of the final decision. The table below provides some descriptive statistics of these variables.

Table 2: **Descriptive statistics of the examination delays of the approved products**

stats	Delay	Ndelay	Edelay
mean	78.18846	29.45385	48.72308
sd	31.13861	23.56413	23.43743
min	38	2	9
max	215	183	180
N	260	260	260

The table 2 shows that the review time is on average higher at European level than at the national level. All rapporteur countries send their draft assessment reports to the European food and safety authority (EFSA). Thus, all drafts are centralised at the European level and lead at the same time, at a strong congestion.

6.2 The explanatory variables

Grant a market approval or not may depend on the inherent factors that affect the review process, such as the role of regulatory factors (the seniority of the active substance and the geographical zones of the rapporteur countries), the risks of pesticide use, the importance of the active substance, the biological activity, and the characteristics of the plant protection firms.

- **The seniority variable**

There are two types of seniority variable, namely, the existing actives substances and the news actives substances. According to our proposition 1 we expect that news actives substances should be reviewed faster than existing actives substances. Indeed, in this empirical investigation, we use existing actives substances as a proxy of the low quality products because they seem to be more risky than the news actives substances. That said the seniority of the active substance is coded by the dummy variable OLD that take the value one for existing active substances and zero new active substances.

- **The geographical zones of the rapporteur countries**

Since June 2011, the EU countries are divided into three zones in which Member States have similar agro-climatic conditions (the European Commission Regulation (2009)). The expected benefits are a reduction of administrative charge and a wider availability of pesticides for European farmers. The main zones of market approval of plant protection products are: the zones North (Denmark, Estonia, Latvia, Lithuania, Finland, and Sweden), Centre (Belgium, Czech Republic, Germany, Ireland, Luxembourg, Hungary, Netherlands, Austria, Poland, Romania, Slovenia, Slovakia, and United Kingdom) and South (Bulgaria, Greece, Spain, France, Italy, Cyprus, Malta, and Portugal). The active substance is approved at European level but the evaluation of the product is made by a rapporteur member state belonging to one of these zones. We code the geographical zones by dummy variables, ZON_i with $i = (ce, no, so)$ as follows:

ZON_{ce}: denotes the rapporteur countries of the centre

ZON_{no}: denotes rapporteur countries of the north

ZON_{so}: denotes rapporteur countries of the south

We normalise on ZON_{ce} and according to our proposition 3, we have no prior expectations regarding the signs of the marginal effects of these variables because we can not evaluate the level of precision of the review in each zone. Nevertheless, we can infer the proposition 3 that a zone which review faster may be a zone with a high level of accuracy, assuming that the approved products are potentially high quality products.

- **Risks of pesticide use**

Again, we use the active substances which are health and environmental consequences worse in expectation compared to the expected benefits as a proxy of low quality products. Consequently, the proposition 1 leads us to expect a longer examination delay for these types of products. This hypothesis is also consistent with the result find by Cropper et al. (1992). They show that the probability that the US Environmental Protection Agency (EPA) will disallow continued use of a pesticide on a particular crop positively related to the risks that pesticide poses to human health and the environment. Thus, the variables carcinogenicity (CAR), toxicity (TOX), genotoxicity ($GENOTOX$) and ecotoxicity ($ECOTOX$) are each, used as a measure of risk. Specifically, each of these variables is a dummy which takes the value one when the active substance presents significant risks for humans and environment and zero otherwise.

- **The importance of the active substance**

We use the economics importance of the treated crop as a measure of the importance of the active substance. In fact, the economic importance here can be thought of as jobs or total GDP share for crops and according to the proposition 2, we expect that the active substances used to treat the most important crops have a faster review time (Dranove and Meltzer, 1994; Regibeau and Rockett, 2010). Thus, we code the importance by the dummy variable $CULT$ which take the value one for a "major crops" and zero otherwise.

- **The geographical origin of firms**

Firms that submit their product for market approval are from Europe, America, Asia and the rest of the world. The dummy variable $ORIG$ denote this geographical origin and take the value one for a European firm and zero

for a foreign firm. It is expected that foreign firm's active substance is reviewed faster than the local firms (Olson, 1997).

- **The biological categories**

Pesticides are classified according their activities. Firstly, Herbicides are pesticides used to kill unwanted plants. Next, Fungicides are chemical compounds or biological organisms used to kill or inhibit fungi. These fungi can cause serious damage of crops. Finally, Insecticides are used against insects. We code the biological category by dummy variables, CAT_i with $i = (fu, hb, in)$ as follows:

CAT_{fu}: for fungicides

CAT_{hb}: for herbicides

CAT_{in}: for insecticides

We normalise on CAT_{hb}. Croll (1991) and Haarstad and Ludvigsen (2007) show that herbicides are the major pesticides that contaminate surface and groundwater in Europe. Thus, they could be reviewed more slowly than other types of pesticides.

7 Results

We will present in the following sections the main results of both standard survival analysis and competing risks models.

7.1 Results for the standard single event time model

Our sample was divided into two sub-samples according to the type of procedure. The first sub-sample is derived from the market approval standard procedure and the second is relative to the market approval accelerated procedure.

We perform here a nonparametric and parametric survival analysis with a total of 257 active substances approved on 300 products reviewed under the standard procedure.

7.1.1 The non-parametric analysis: Kaplan-Meier estimator

The Kaplan-Meier estimator (1958), also known as the product limit estimator, is an estimator for estimating the survival function from lifetime data. It is the first exploration of the covariates effects and of the distribution to be used in the parametric analysis. Some graphical and statistical tests are made in order to bring out influential classification variables and distribution forms. The Kaplan-Meier estimate of survival and hazard functions are presented in the figures 4 and 5.

The estimate of the survival function (Figure 4) shows two trends. It is constant before 38 months with a probability of survival equal to one and decreasing thereafter. In other words, up to 38 months, no market approval granted. But beyond that, the chances of survival are becoming weaker, corresponding to market approvals granted over time.

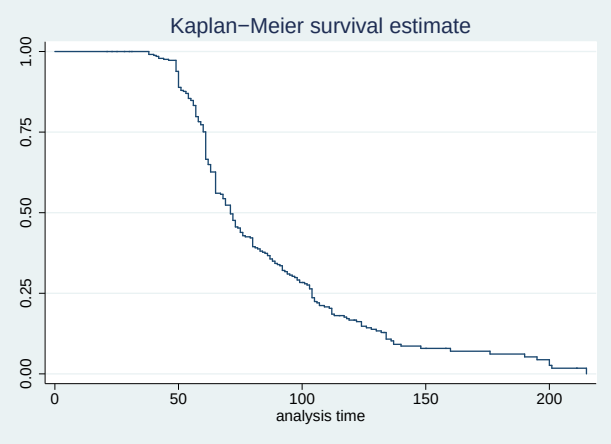


Figure 4: Kaplan-Meier survival functions

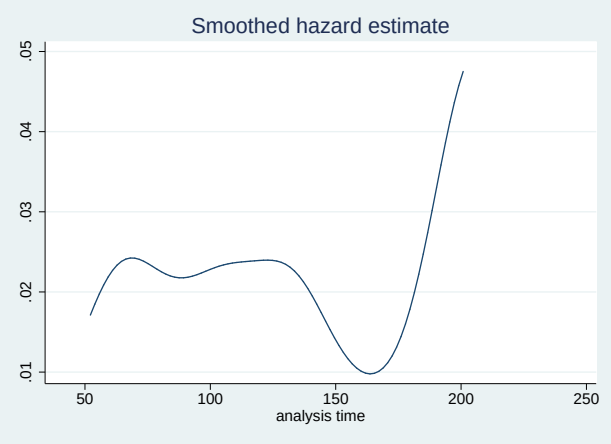


Figure 5: Kaplan-Meier hazard functions

Furthermore, the estimated hazard function (Figure 5) shows a non-monotonic pattern of duration dependence. More specifically, the instantaneous risk of occurrence of a market approval rises from 50 to 70 months and then falls to rise. It rises again from 100 months to 130 months and falls to rise. The dips are so much between 130 and 180 months. This observation may be explained by the fact that in our data there are about 16 active substances with a review time greater than 120 months. These are mostly products of list A1 i.e. the most toxic existing active substances. Thus, these are cases where the regulator makes a "stringent" request that is difficult to fulfill by the firm. Moreover, the non-monotonic form of the hazard curve suggests that non-monotonic distributions (loglogistic and log-normal) will be appropriate distributions in a fully-parametric model.

7.1.2 The parametric analysis

Parametric models which permit the incorporation of the covariates effects are written in a variety of ways such as the proportional hazards metric and the accelerated failure-time metric. The first metric assumes a direct effect on duration, while in the second metric a multiplicative effect of covariates on a baseline hazard function is assumed.

We consider here parametric modeling based on underlying distributions that allow for non-monotone hazard functions according to the Kaplan-Meier results. Thus, the accelerated failure time models with the log-normal and log-logistic distributions are estimated. In order to test the robustness of our parametric specifications we also considered the familiar Weibull model. The table 3 shows the results of estimates. In these models of accelerated life, the positive (negative) coefficient implies that a duration increases (decreases) with changes in values of variables. The values of the Bayesian information criteria (BIC) are also given in this table. These results show that the insecticides (CAT_{in}) obtain a market approval much faster than herbicides (CAT_{hb}). Active substances with significant risk of cancer (CAR), toxicity (TOX) and genotoxicity ($GENOTOX$) are approved less quickly than those which are less risky. The effect of the variable ecotoxicity ($ECOTOX$) is not significant. The products of the local firms are approved more quickly. These results suggest that there exist an approval threshold which may rise if we have a larger welfare loss potentially associated with low quality products. For the herbicides products, the regulator may raise the approval threshold compared to the insecticides. He does this because Herbicides are a major substance that contaminates surface and groundwater in Europe (Croll, 1991; Haarstad and Ludvigsen,

Table 3: parametric estimates

	Weibull	Lognormal	Loglogistic	Gamma
CAT_{hb}	Ref	Ref	Ref	Ref
CAT_{fu}	-0.037	0.010	-0.017	-0.016
	(0.05)	(0.05)	(0.04)	(0.04)
CAT_{in}	-0.142**	-0.069	-0.057	-0.044
	(0.06)	(0.05)	(0.04)	(0.04)
ZON_{ce}	Ref	Ref	Ref	Ref
ZON_{no}	0.072	0.035	0.054	-0.016
	(0.07)	(0.06)	(0.06)	(0.05)
ZON_{so}	0.122**	0.097**	0.131***	0.079**
	(0.05)	(0.04)	(0.04)	(0.04)
$CULT$	0.050	0.048	0.047	0.027
	(0.05)	(0.05)	(0.04)	(0.04)
OLD	-0.016	-0.041	-0.136***	-0.049
	(0.05)	(0.04)	(0.04)	(0.04)
$ORIG$	-0.188***	-0.101**	-0.099**	-0.104***
	(0.05)	(0.04)	(0.04)	(0.04)
TOX	0.055	0.072	0.084**	0.103***
	(0.05)	(0.04)	(0.04)	(0.03)
$ECOTOX$	0.038	0.032	0.022	0.016
	(0.06)	(0.05)	(0.04)	(0.04)
$GENOTOX$	0.238	0.393**	0.448***	0.545***
	(0.19)	(0.18)	(0.14)	(0.14)
CAR	0.152**	0.134**	0.108**	0.135***
	(0.06)	(0.06)	(0.05)	(0.05)
$SAME$	0.161***	0.040	0.026	0.001
	(0.06)	(0.05)	(0.05)	(0.04)
$size$	-8.42e-07*	6.97e-07	-5.22e-07	-7.55e-07*
	(0.00)	(0.00)	(0.00)	(0.00)
sub	0.038***	0.032***	0.043***	0.027***
	(0.01)	(0.01)	(0.01)	(0.00)
$experience$	0.011***		0.008***	0.008***
	(0.00)		(0.00)	(0.00)
$cons$	4.280***	4.158***	4.136***	4.066***
	(0.08)	(0.08)	(0.07)	(0.07)
bic	251.583	193.138	147.645	133.376
N	260.000	260.000	260.000	260.000

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

2007).

For the carcinogen, the toxicity and the genotox variables, it makes sense to argue that this approval threshold is higher, while for the ORIG variable´ s opposite results it makes sense to argue that the approval threshold is lower. In other words, for these, the approval threshold would be influenced by the welfare gain or loss of the substance. For the variable origin of the firm ($ORIG$), since the welfare gain/loss includes the profit of the entity submitting the substance, for European firms the gains are larger and the losses are smaller for approval. Contrary to (Olson, 1997), we don't find any evidence that the review is faster for the European firms because they know the system better. Indeed, in our results, the coefficient of the experience variable which measures the number of past submissions is significant and positive. Moreover, for the more toxic substances that potentially cause serious diseases, the welfare gain is smaller compared to the loss from approval (Cropper et al., 1992). About the geographical zone of the rapporteur country, the center zone review faster. In this zone there are two giant plant protection products firms, that is BAYER and BASF.

This is a learning effect of the large firms with presumably a lot of experience and dedicated staff to handle approvals. The variable $SAME$ which capture the idea that the rapporteur country and the firm have an identical nationality have a positive coefficient but only significant with the weibull distribution. This positive coefficient seems to show that there is no bias in the approval process when the rapporteur country and the firm have an identical nationality.

Also, the result seem to show that the existing active substances obtain a market approval much faster than news products (see the OLD variable). However, when we split our approval process in two procedures: a national procedure (see table 4) and a European procedure (see table 5), we find different results. For the national procedure, new active substances are reviewed faster. This is consistent with our proposition 1.

Table 4: parametric estimates of the national phase

	Weibull	Lognormal	Loglogistic	Gamma
CAT_{hb}	Ref	Ref	Ref	Ref
CAT_{fu}	-0.085	-0.092	-0.099	-0.115
	(0.08)	(0.08)	(0.07)	(0.08)
CAT_{in}	-0.209**	-0.074	-0.026	-0.079
	(0.09)	(0.09)	(0.08)	(0.09)
ZON_{ce}	Ref	Ref	Ref	Ref
ZON_{no}	0.031	-0.089	-0.088	-0.080
	(0.12)	(0.11)	(0.10)	(0.11)
ZON_{so}	0.159**	0.095	0.138**	0.124*
	(0.08)	(0.07)	(0.06)	(0.07)
$CULT$	0.087	0.054	0.037	0.052
	(0.08)	(0.08)	(0.07)	(0.08)
OLD	0.301***	0.224***	0.072	0.180**
	(0.08)	(0.08)	(0.07)	(0.08)
$ORIG$	-0.297***	-0.070	-0.030	-0.091
	(0.08)	(0.08)	(0.07)	(0.08)
TOX	0.011	0.091	0.112*	0.104
	(0.08)	(0.08)	(0.06)	(0.08)
$ECOTOX$	-0.079	-0.131	-0.139*	-0.134
	(0.09)	(0.09)	(0.07)	(0.09)
$GENOTOX$	-0.350	-0.093	-0.030	-0.067
	(0.32)	(0.31)	(0.23)	(0.31)
CAR	0.068	0.023	-0.021	0.029
	(0.11)	(0.10)	(0.09)	(0.10)
$SAME$	0.151	0.030	-0.043	0.048
	(0.10)	(0.10)	(0.08)	(0.09)
$size$	-1.75e-06**	2.58e-07	-1.07e-06	-1.15e-06
	(8.75e-07)	(7.55e-07)	(7.34e-07)	(8.51e-07)
sub	0.028**	0.034***	0.043***	0.038***
	(0.01)	(0.01)	(0.01)	(0.01)
$experience$	0.015***		0.006*	0.009***
	(0.00)		(0.00)	(0.00)
$cons$	3.298***	3.075***	3.127***	3.069***
	(0.14)	(0.13)	(0.12)	(0.13)
bic	538.975	486.682	442.851	486.575
N	260.000	260.000	260.000	260.000

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Table 5: parametric estimates of the European phase

	Weibull	Lognormal	Loglogistic	Gamma
CAT_{hb}	Ref	Ref	Ref	Ref
CAT_{fu}	0.070	0.063	0.011	0.045
	(0.07)	(0.06)	(0.06)	(0.06)
CAT_{in}	-0.026	-0.058	-0.062	-0.060
	(0.07)	(0.07)	(0.07)	(0.07)
ZON_{ce}	Ref	Ref	Ref	Ref
ZON_{no}	0.064	0.166*	0.170**	0.178**
	(0.09)	(0.09)	(0.08)	(0.09)
ZON_{so}	0.101	0.099*	0.129**	0.122**
	(0.06)	(0.06)	(0.06)	(0.06)
$CULT$	0.018	0.037	0.024	0.037
	(0.06)	(0.06)	(0.06)	(0.06)
OLD	-0.210***	-0.249***	-0.276***	-0.288***
	(0.06)	(0.06)	(0.06)	(0.06)
$ORIG$	-0.066	-0.099	-0.099*	-0.118*
	(0.06)	(0.06)	(0.06)	(0.06)
TOX	0.128*	0.088	0.057	0.102*
	(0.07)	(0.06)	(0.06)	(0.06)
$ECOTOX$	0.093	0.101	0.131**	0.095
	(0.07)	(0.07)	(0.07)	(0.07)
$GENOTOX$	0.483**	0.706***	0.741***	0.745***
	(0.24)	(0.25)	(0.20)	(0.24)
CAR	0.243***	0.182**	0.161**	0.186**
	(0.08)	(0.08)	(0.08)	(0.08)
$SAME$	0.107	0.041	0.028	0.054
	(0.08)	(0.07)	(0.07)	(0.07)
$size$	-5.11e-07	1.20e-06**	2.49e-08	1.11e-07
	(6.76e-07)	(5.93e-07)	(6.48e-07)	(6.66e-07)
sub	0.041***	0.036***	0.043***	0.039***
	(0.01)	(0.01)	(0.01)	(0.01)
$experience$	0.008***		0.008***	0.007***
	(0.00)		(0.00)	(0.00)
$cons$	3.779***	3.654***	3.626***	3.638***
	(0.10)	(0.11)	(0.10)	(0.11)
bic	400.999	361.624	352.486	360.964
N	260.000	260.000	260.000	260.000

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Our intuition here is that, OLD variable does not influence the threshold but may influence the effort put in if the profit gains from an older substance are more modest than for a new substance. In fact, most patents for existing products have expired and then, several companies may offer generic products that compete with those

existing products. Thus, the patent holders of these existing products may be less incited to invest money to make their products comply with the new standard of regulation since the expected payoffs are low. In other words, effort is larger for news active substances because the expected payoff is higher. This effort involved in speeding up the review process (Regibeau and Rockett, 2010). The result of our variable sub i.e. the number of submission is consistent with this finding. For the European procedure, existing active substances are reviewed faster. We think that these old active substances are reviewed quickly because they have previously been approved in accordance with the old approval standard i.e. the European Commission Directive (1991). So, they know better this type of application.

As we said before, we divide the review process into national and European phases because the covariates may affect differently the examination delays of active substances depending on whether the product is reviewed either at the national level or the European level. Remember that, the national phase is relative to the examination of the active substance made by the rapporteur member state which writes a review report including a recommendation about the inclusion or not in Annex I. The European phase is about the review conducted both by the European Food Safety Authority and the European commission and which leads to a final decision. Tables 4 and 5 show the results of this analysis.

Moreover, some covariates don't affect the national and European phases in the same manner. That is the case for the $ECOTOX$ variable which is negative and significant in the national phase (but the effect is not significant), however, it is positive and significant in the European phase. In other words, ecotoxic products are approved faster at the national level but slowly at the EU level. For the regulator at the national level, the ecotoxicity may be an indicator of the efficiency of the product. That is why the national authorities review quickly the ecotoxic products but they make recommendations for the use. Also, at the national level, products of larger firms are approved much faster. These results may suggest that larger firms lobbying more at the national level. But, this finding need to be investigated more in order to have a more precise argument for bias or lack of bias at the local or EU approval level.

7.2 The results of the model on cause-specific hazards

In our standard survival analysis, the risk set is defined as the group of products that have not experienced the approval event and therefore are at risk for this event of interest at time t. However, some Products may have a competing event as the rejection.

That is why, in the manner of the cause-specific hazards, a proportional hazards model is developed separately for each event type in which products which experience the competing event are treated as censored observations. Since the likelihood may be written such that the competing event is treated as a censored event, this cause-specific hazards model is exactly the same as what some investigators model when "ignoring" competing events.

The Table 6 below shows the main results of estimating a Cox model. In this Cox regression, we specify respectively, approval as the event of interest and rejection and withdrawal as the competing events, rejection as the event of interest and approval and withdrawal as the competing events, and finally, withdrawal as the event of interest and approval and rejection as the competing events. Here, a covariate with a negative coefficient will reduce the hazard rate and as a consequence increase survival and the examination delays.

Table 6: cause-specific hazards estimates

	Approved products	Rejected products	Withdrawn products
CAT_{hb}	Ref	Ref	Ref
CAT_{fu}	0.007	-0.533	-0.850
	(0.16)	(0.41)	(0.86)
CAT_{in}	0.214	0.462	0.297
	(0.17)	(0.38)	(0.77)
ZON_{ce}	Ref	Ref	Ref
ZON_{no}	0.358	-45.793	-44.583
	(0.23)	(.)	(.)
ZON_{so}	-0.181	0.176	1.037
	(0.15)	(0.30)	(0.89)
$CULT$	0.103	0.056	-1.773**
	(0.15)	(0.32)	(0.71)
OLD	-0.100	2.231***	0.853
	(0.15)	(0.74)	(0.96)
$ORIG$	0.538***	-0.636*	-1.432
	(0.16)	(0.34)	(0.90)
TOX	-0.207	0.397	-0.230
	(0.16)	(0.32)	(0.77)
$ECOTOX$	0.036	-0.035	-3.411***
	(0.17)	(0.44)	(1.05)
$GENOTOX$	-1.009*	1.720***	-38.576
	(0.60)	(0.47)	(.)
CAR	-0.391*	0.535	-0.912
	(0.20)	(0.34)	(0.88)
$SAME$	-0.029	-0.399	0.370
	(0.19)	(0.55)	(1.26)
$size$	-0.000**	-0.000	-0.000
	(0.00)	(0.00)	(0.00)
sub	-3.12e-06***	-5.28e-06**	-2.74e-06
	(1.47e-06)	(3.63e-06)	(9.35e-06)
N	327.000	327.000	327.000
N_{fail}	260.000	52.000	15.000

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

The results show that, the time to withdrawal is faster for the active substances use for important crops ($CULT$). The effect is not significant for both approval and rejection events.

About the seniority variable (OLD), news active substances are approved quickly than existing active substances (but the effect is not significant).

Table 7: Fine and Gray estimates

	Approval event	Rejection event	Withdrawal event
CAT_{hb}	Ref	Ref	Ref
CAT_{fu}	0.142	-0.294	-0.190
	(0.15)	(0.41)	(0.77)
CAT_{in}	0.123	0.281	-0.421
	(0.18)	(0.40)	(0.80)
ZON_{ce}	Ref	Ref	Ref
ZON_{no}	0.580**	-18.729***	-18.048***
	(0.19)	(0.33)	(0.55)
ZON_{so}	-0.262*	0.246	-0.019
	(0.15)	(0.29)	(0.52)
$CULT$	0.112	-0.074	-1.218*
	(0.16)	(0.34)	(0.67)
OLD	-0.431***	2.263**	0.672
	(0.14)	(0.72)	(0.69)
$ORIG$	0.648***	-0.940***	-0.835
	(0.16)	(0.34)	(0.55)
TOX	-0.301**	0.381	0.145
	(0.15)	(0.32)	(0.62)
$ECOTOX$	0.236	0.228	-1.389**
	(0.19)	(0.47)	(0.60)
$GENOTOX$	-1.615***	1.864***	-18.085***
	(0.50)	(0.41)	(0.92)
CAR	-0.463***	0.652*	-0.152
	(0.18)	(0.35)	(0.79)
$SAME$	-0.006	-0.342	-1.022
	(0.18)	(0.60)	(1.18)
$size$	-1.08e-06	-2.53e-06	9.00e-07
	(1.41e-06)	(3.16e-06)	(7.29e-06)
sub	-0.048*	-0.043	-0.253
	(0.02)	(0.03)	(0.19)
N	327.000	327.000	327.000
N_{fail}	260.000	52.000	15.000

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

They are both rejected and withdraw slowly than old products. Active substances with significant risk of cancer (CAR), ecotoxicity ($ECOTOX$) and genotoxicity ($GENOTOX$) are both approved and withdraw less quickly than those which are less risky. They are rejected faster. These results are consistent with our previous findings.

7.3 The results of the model on a subdistribution hazards

In contrast to the cause-specific hazards model that eliminates products which have the competing event, the subdistribution hazards model due to Fine and Gray (1999), were constructed so that they include both products without any event and those which have had the competing event. This model is based on the proportional hazards assumptions.

The table 7 shows the results when we focus on the risk of approval and treat rejection as the competing event. This table shows the exponentiated coefficients estimates known as subhazard ratios. A positive (negative) coefficient means that the effect of increasing that covariate is to increase (decrease) the subhazard and thus increase (decrease) the Cumulative Incidence Function across the board. Clearly, the interpretation of this subhazard ratio is similar to the interpretation of the hazard ratio in the Cox model, but the interest here is focused on the cumulative incidence function rather than the survival function.

The news active substances have a higher incidence of approval than the existing active substances. But, the existing active substances have a higher incidence of both rejection and withdrawal (but the effect is not significant for withdrawal) than the news active substances. This is consistent with our previous finding, especially for the

national procedure. Similarly, the zone north (ZON_{no}) have a higher incidence of approval than the zone centre (ZON_{ce}), but the zone centre have a higher incidence of both rejection and withdrawal than the zone north.

Furthermore, important crops ($CULT$) have a higher incidence of approval than the other crops (the effect is not significant). But they have a lower incidence of both rejection and withdrawal than the others crops. This result suggests that the review process could be influenced by some economic considerations due to the economic importance of certain crops. However, in the administrative procedure, it is assumed that there is no economic consideration.

For the variable $ORIG$, the products for the European countries have a higher incidence of approval than the products for the foreign countries, but they have a lower incidence of both rejection and withdrawal than the products of the foreign countries. This is consistent our results in the standard survival analysis.

Finally, toxic (TOX), genotoxic ($GENOTOX$), and carcinogen (CAR) products have a higher incidence of both rejection and withdrawal (effect is not significant for carcinogen products) than the others (significant effect) but lower incidence of approval (effect is not significant for toxic products). However, dangerous active substances for the environment ($ecotox$) have a higher incidence of both approval and rejection than the others (the effect is not significant), but a lower incidence of withdrawal.

7.4 Conclusion

In this paper, we analyse empirically the main determinants of market approval delays of plant protection active substances in Europe. The process is framed by the European Commission Regulation (2009) concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. One interesting feature of this regulation is that it is based both on a decentralized examination by rapporteur country and on a centralized examination by the EFSA. Our econometric analysis is based on both standard survival and competing risks models. The data covers 327 active ingredients reviewed between 1993 and 2013.

We find that the insecticides obtain a market approval much faster than herbicides. Active substances with significant risk of cancer, toxicity and genotoxicity are approved less quickly than those which are less risky. The effect of the variable ecotoxicity is not significant. The process is faster for larger firms. The products of the local firms are approved more quickly. These results suggest that there exist an approval threshold which may rise if we have a larger welfare loss potentially associated with bad products. For the herbicides products, the regulator may raise the approval threshold compared to the insecticides. For the carcinogen, the toxicity and the genotoxicity variables, it makes sense to argue that this approval threshold is higher, while for the origin of the firm variable opposite results it makes sense to argue that the approval threshold is lower. In other words, for these, the approval threshold would be influenced by the welfare gain or loss of the substance. For the origin variable, since the welfare gain/loss includes the profit of the entity submitting the substance, for European firms the gains are larger and the losses are smaller for approval.

Otherwise, the center zone reviews faster. In this zone there are two giant plant protection products firms, that is BAYER and BASF. This is a learning effect of the large firms with presumably a lot of experience and dedicated staff to handle approvals. The ecotoxic products are approved faster at the national level bat slowly at the EU level. In fact, for the regulator at the national level, the ecotoxicity may be an indicator of the efficiency of the product.

Also, the result shows that the new active substances obtain a market approval much faster than existing products. However, for the national procedure, existing active substances are reviewed faster. The intuition here is that, seniority variable does not influence the threshold but may influence the effort put in if the profit gains from an older substance are more modest than for a new substance. This lower effort involved in lower review process.

When we divide the entire process in national and European phases, we find that, the size variable only affect the national level with a negative and significant coefficient, and variables ORIG, genotox, carcinogen and same that have only an effect on the European phase. At this European level, products of local firms are approved much faster. These results may suggest that larger firms lobbying more at the national level and the European firms lobbying more at the European level. But, this finding need to be investigated more in order to have a more precise argument for bias or lack of bias at the local or EU approval level.

Finally, the results of our competing risks analysis are consistent with the results of our standard survival analysis. Nevertheless, the results suggest that the review process could be influenced by some economic considerations due to the economic importance of certain crops. However, in the administrative procedure, it is assumed that there is no economic consideration.

These results suggest that the European authorities, wanting to ensure the health and environmental safety can be strict in terms of market approval of plant protection active substances. This may have on the one hand, a positive impact on innovation because; a stricter regulation may be market entry barrier. In doing so, it reduces the competitive pressure for local firms and allows them to invest more resources in risky innovation activities assuming a rather high level of competition intensity. On the other hand, this stricter regulation may have a negative impact on innovation since market entry barriers make it very difficult for innovative foreign firms to enter markets, which is negative for the overall innovative performance in these markets, especially if the competition intensity is still rather low.

Bibliography

Aghion, P., Blundell, R., Griffith, R., Howitt, P., and Prantl, S. (2009). The Effects of Entry on Incumbent Innovation and Productivity. *Review of Economics and Statistics*, 91(1):20–32.

CAST (1981). Impact of Government Regulation on the Development of Chemical Pesticides for Agriculture and Forestry. *Ames, Iowa: Council for Agricultural Science and Technology.*

Croll, B. (1991). Pesticides in Surface Waters and Groundwaters. *Journal of the Institution of Water and Environmental Management*, 5(4):389–395.

Cropper, M., Evans, W., Berardi, S., Duclasoares, M., and Portney, P. (1992). The Determinants of Pesticide Regulation - A Statistical -Analysis of EPA Decision-Making. *Journal of Political Economy*, 100(1):175–197.

Dean, T., Brown, R., and Stango, V. (2000). Environmental regulation as a barrier to the formation of small manufacturing establishments: A longitudinal examination. *Journal of Environmental Economics and Management*, 40(1):56–75.

Directive (1991). Directive 91/414/EEC - plant protection products of 15 July 1991 concerning the placing of plant protection products on the market. *Official Journal of the European Union*.

Dranove, D. and Meltzer, D. (1994). Do Important Drugs Reach the Market Sooner. *Rand Journal of Economics*, 25(3):402–423.

Fine, J. and Gray, R. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*, 94(446):496–509.

Haarstad, K. and Ludvigsen, G. H. (2007). Ten years of pesticide monitoring in Norwegian ground water. *Ground Water Monitoring and Remediation*, 27(3):75–89.

Harhoff, D. and Wagner, S. (2009). The Duration of Patent Examination at the European Patent Office. *Management Science*, 55(12):1969–1984.

Helland, E. and Matsuno, M. (2003). Pollution abatement as a barrier to entry. *Journal of Regulatory Economics*, 24(2):243–259.

Klapper, L., Laeven, L., and Rajan, R. (2006). Entry regulation as a barrier to entrepreneurship. *Journal of Financial Economics*, 82(3):591–629.

Olson, M. (1997). Characteristics and the speed of FDA approval. *Journal of Economics & Management Strategy*, 6(2):377–401.

Prantl, S. (2012). The impact of firm entry regulation on long-living entrants. *Small Business Economics*, 39(1):61–76.

Regibeau, P. and Rockett, K. (2010). Innovation Cycles and Learning at the Patent Office: Does the Early Patent Get the Delay? *Journal of Industrial Economics*, 58(2):222–246.

Regulation (2008). COMMISSION REGULATION (EC) No 33/2008 of 17 January 2008 laying down detailed rules for the application of Council Directive 91/414/EEC as regards a regular and an accelerated procedure for the assessment of active substances which were part of the programme of work referred to in Article 8(2) of that Directive but have not been included into its Annex I. *Official Journal of the European Union*.

Regulation (2009). Regulation (ec) no 1107/2009 of the european parliament and of the council of 21 october 2009 concerning the placing of plant protection products on the market and repealing council directives 79/117/eec and 91/414/eec. *Official Journal of the European Union*.

Upton, H. (1982). The Impact of Regulatory Delay on R&D Productivity and Costs in the Pesticide Industry. *Ph.D. dissertation. University of Minnesota, St. Paul*.

Xie, Y. and Giles, D. E. (2011). A survival analysis of the approval of US patent applications. *Applied Economics*, 43(11):1375–1384.