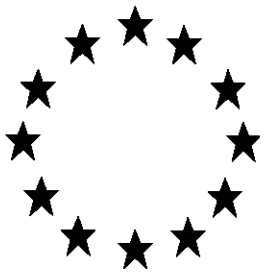
Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report[i]



Ethyl butylacetylaminopropionate

Product-type 19
(insect repellent)

March 13 2014

Belgium

Ethyl butylacetylaminopropionate (PT19)

Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on March 13th, 2014

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1 STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1 PRINCIPLE OF EVALUATION

This assessment report has been established as a result of the evaluation of Ethyl butylacetylaminopropionate, furthermore referred to as IR3535®, as product-type 19 (insect repellent), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with a view to the possible inclusion of this substance into Annex I or IA to that Directive.

The evaluation has therefore been conducted in the view to determine whether it may be expected, in light of the common principles laid down in Annex VI to Directive 98/8/EC, that there are products in product-type 19 containing IR3535® that will fulfil the requirements laid down in Article 5(1) b), c) and d) of that Directive.

1.2 PURPOSE OF THE ASSESSMENT

The aim of the assessment report is to support a decision on the approval of IR3535® for product-type 19, and should it be approved, to facilitate the authorisation of individual biocidal products in product-type 19 that contain IR3535®. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

The conclusions of this report were reached within the framework of the uses that were proposed and supported by the applicant. Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Regulation (EU) No 528/2012.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

1.3 PROCEDURE FOLLOWED

This assessment report has been established as a result of the evaluation of Ethyl butylacetylaminopropionate, furthermore referred to as IR3535®, product-type 19 (Insect

[1] Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

Repellent), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[2].

IR3535® (CAS no. 52304-36-6) was notified as an existing active substance, by Merck KGaA, hereafter referred to as the applicant, in product-type 19.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[3] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 7(1) of that Regulation, Belgium was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for IR3535® as an active substance in Product Type 19 was April 30th 2006, in accordance with Annex V of Regulation (EC) No 1451/2007.

On 27/04/2006, Belgian competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 27/07/2006.

On 05/11/2009, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 10/12/2009. The competent authority report included a recommendation for the inclusion of IR3535®in Annex I to the Directive for product-type 19.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on 16/12/2009. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on March 13th 2014.

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2 Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

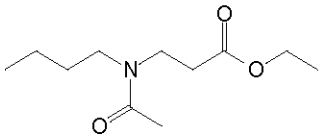
3 Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

2 OVERALL SUMMARY AND CONCLUSIONS

2.1 PRESENTATION OF THE ACTIVE SUBSTANCE

2.1.1 Identity, Physico-Chemical Properties & Methods of Analysis

2.1.1.1 Identity

CAS-No.	52304-36-6
EINECS-No.	257-835-0
Other No. (CIPAC, ELINCS)	CIPAC No.: 667
IUPAC Name	ethyl 3-[N-acetyl-N-butyl] aminopropionate
Common name, Synonym	IR3535®, Ethyl butylacetylaminopropionate, ethyl N-acetyl-N-butyl-β-alaninate (EINECS)
Molecular formula	$C_{11}H_{21}NO_3$
Structural formula	
Molecular weight (g/mol)	215.29 g/mol
Purity of a.s.	> 99 % w/w

2.1.1.2 Physico-Chemical Properties

IR3535® as manufactured is a clear colourless liquid. The relative density of IR3535® is 0.998 at 20 °C and the melting point is found to be less than -90 °C. The observed vapour pressure is 0.15 Pa at 20 °C.

In non-buffered water at 20 °C a solubility of 70 g/L is measured for IR3535®. A water solubility at pH 5 of 69.92 g/L, at pH 7 of 56.72 g/L and at pH 9 of 68.0 g/L is found at 20 °C ± 1 °C. At pH 9 the test item was unstable due to hydrolysis. The given result is assumed to reflect the equilibrium between hydrolysis and solubility. The substance is also soluble in organic solvents. IR3535® is not ionisable and therefore cannot dissociate in water.

A Henry's law constant of 4.613 x 10^{-4} $Pa.m^3.mol^{-1}$ is calculated which indicates that volatilisation is not expected to significantly contribute to the dissipation of IR3535® in the environment.

The log Pow was measured by HPLC to be 1.7 at 23-24 °C, which indicates no potential for IR3535® to bioaccumulate. IR3535®is stable at room temperature, is not highly flammable and has a flash point of 159 °C. The substance is not considered explosive or oxidizing and has a surface tension of 59.6 mN/m (aqueous solution (1 g/L) at 20 °C).

The information contained in the mass spectrum, the infrared spectrum, the UV spectrum and the magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) are consistent with the structure of IR3535®, Ethyl 3-[N-acetyl-N-butyl] aminopropionate.

2.1.1.3 Methods of Analysis

The content of IR3535® and the impurities can be determined by an analytical method based on gas-chromatography using FI detection to detect and quantify the active ingredient and the impurities. An analytical method based on Ultra Performance Liquid Chromatography with mass spectrometric detection (UPLC-MS/MS) is available for the detection after solid phase extraction (SPE) of the active ingredient in water.

An analytical method for the formulation has to be developed for specific formulations and not for a model formulation. Therefore, an analytical method for the detection and identification of IR3535® in formulations is not submitted, this point will be addressed in the national registrations for the specific formulations.

2.1.2 Intended Uses and Efficacy

IR3535® has been evaluated for its use as an insect repellent belonging to Product Type 19 according to Annex V of the Directive 98/08/EC.

The active substance IR3535® is mainly used at concentrations ranging from 6 to 20 % in lotions and pump sprays. IR3535® is actually considered as an insect repellent to protect humans from insects by application on skin or hair. However, no efficacy tests were provided to support efficacy claims for treated articles and clothing.

IR3535® acts as a repellent and efficacy has been demonstrated against:

Mosquitoes: *Anopheles sp.*; *Aedes sp.* and *Culex sp.*
Sand flies: *Phlebotomus sp.*
Ticks: *Ixodes sp.*
Lice: *Pediculus sp.*
Flies: *Stomoxys sp.*
Wasps: *Pollistes sp.*
Bees: *Apis sp.*

To support other claims (for example: against other organisms or to protect animals), new information or data from robust studies should be supplied at the product authorisation stage.

The mode of action of IR3535® is not a passive masking of an attracting odour of a victim, but an active repellent effect as insects avoid entering regions with IR3535® vapours. The exact

biochemical mode of action of IR3535® on insects is not well known yet, but it is most self-evident to assume that IR3535® has an olfactory-based effect.

As the active substance IR3535® is a repellent (no killing action) and does not give rise to selection pressure, no resistance can be developed.

Full/ robust efficacy studies for all claimed target organisms for IR3535®-based formulations are required at the Product Authorisation Stage.

2.1.3 Classification and Labelling

2.1.3.1 Proposal for the Classification and Labelling of the Active Substance

Classification	According to Directive 67/548/EEC
Hazard Symbol	None
R phrases	None
S phrases	None

Classification	According to CLP-Regulation (EC) No 1272/2008
GHS Pictograms	 GHS07
Signal Word	Warning
Hazard Class and Category Codes	Irritating to eyes, Category 2
Hazard Statement Codes	H319: Causes serious eye irritation
Prevention Precautionary Statement Codes	P280: Wear protective gloves/protective clothing/eye protection/face protection P305+351+338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses if present and easy to do – continue rinsing P337+313: If eye irritation persists get medical advice/attention

2.1.3.2 Proposal for the Classification and Labelling of the (dummy) Biocidal Product

This is a model formulation; a current classification is not available. A proposed classification is given below.

Proposed classification biocidal product: water/ethanol-based 20 % IR3535® model pump-spray formulation.

Classification	According to Directive 67/548/EEC
Class of danger	Xi
R phrases	R10 Flammable R36 Irritating to eyes
S phrases	

Classification	According to CLP-Regulation (EC) No 1272/2008
GHS Pictograms	GHS02 GHS07
Signal Word	Warning
Hazard Class and Category Codes	Flammable Liquid, category 3 Irritating to eyes, category 2
Hazard Statement Codes	H226 Flammable liquid and vapour H319 Causes serious eye irritation
Prevention Precautionary Statement Codes	P210, P233, P240, P241, P242, P243, P280 P264, 280 P305 + P351 + P338 + P337 + P313
Response Precautionary Statement Codes	P203 + P361 + P353 + P370 + P378 P305 + P351 + P338 + P337 + P313
Disposal Precautionary Statement Codes	P501

2.1.3.3 Justification for the proposal

Ethyl 3-[N-acetyl-N-butyl] aminopropionate (IR3535®) is not included in Annex I, according to the last ATP (29th) of Directive 67/548/EEC.

There is not yet a harmonized classification for Ethyl 3-[N-acetyl-N-butyl] aminopropionate (IR3535®) according to CLP-Regulation (EC) No 1272/2008.

IR3535® caused mild eye irritation in the rabbit which was reversible and does not imply classification according to Directive 67/548/EC. Due to the stricter cut-off values in the CLP-Regulation (EC) No 1272/2008, IR3535® should be classified as an eye irritant (Category 2).

2.2 SUMMARY OF THE RISK ASSESSMENT

2.2.1 Human Health Risk Assessment

2.2.1.1 Hazard Identification

2.2.1.1.1 Hazard Identification of the Active Substance IR3535®

ADME

The ADME- studies show that oral and intravenous administration of IR3535® is followed by a rapid and extensive absorption in the rat, rabbit, and dog. Thus, no correction for incomplete oral absorption is necessary in the risk assessment. The substance is quickly distributed throughout the body tissues. The majority of the administered dose is excreted rapidly mainly via urine. There are no indications of accumulation in any tissue. IR3535® is efficiently metabolised. The major metabolic pathway of IR3535® is by hydrolysis at its ester moiety to the respective carboxylic acid: N-acetyl-N-butyl-3-aminopropionic acid. The metabolism of IR3535® in rat, rabbit, dog, and man was comparable. ADME-studies show that after dermal application, IR3535® is mainly excreted via urine and to a lesser extent via faeces. Highest concentrations of IR3535® were found at the application site, in the excretion organs kidney and liver as well as in blood/plasma indicating that IR3535® was distributed evenly over the body. Dermal absorption was studied in the rat and rabbit, using human tissue, and in human volunteers. For the pure active substance and previously studied cream formulations our conclusions on dermal penetration are based on the *in vivo* animal studies and the human skin *in vitro* study. For a 24 hour application, a dermal penetration of 50 % was determined. For a more typical use pattern of 10 hours, a less reliable dermal penetration of 30 % was determined/extrapolated for the previously studied cream formulations. However, for water/ethanol-based 20 % IR3535® market formulations a dermal penetration of 14 % was determined for a 12 hour exposure (~ typical use condition of 10 hours) based on the outcome of the human volunteer study. Based on the findings of this study, a dermal absorption of 14 % is also valid for an exposure of 24 hours. The water/ethanol-based 20 % IR3535® market spray formulation used in this volunteer study represents a worst case formulation with regard to skin penetration (main component is ethanol, and in addition contains other well known enhancers of skin penetrating properties of substances). Therefore, a dermal absorption of 14 % derived from this study is also relevant for 20 % IR3535® lotion/cream formulations. The **dermal penetration of 14 %** supported by *in vivo* human data is used for the human health risk assessment.

Acute toxicity

In acute toxicity studies, IR3535® was found of low oral, dermal, and inhalation toxicity when the rat was used as the test species. Clinical symptoms recorded after oral administration, were incomplete eyelid closure, salivation, locomotor disturbance 1-15 min. after treatment and lasting up to d2. After dermal administration, local effects were characterised by pronounced

erythema but which was reversible. Local effects after inhalation were characterised by irritation of the respiratory tract: irregular, accelerated, intermittent respiration, bloody discharge at the nose.

Irritation and sensitisation

IR3535® has no potential for skin irritation and is not sensitising to the skin. . In the (older and not in compliance with OECD guideline 404) dermal studies performed with the undiluted active substance, as well as in the dermal irritation studies performed with a 10 % IR3535® formulation in rabbits and in human volunteers, IR3535® and 10 % IR3535® did not produce dermal irritation. RMS is of the opinion that the data available is adequate enough to support the conclusion that IR3535®is not a skin irritant. IR3535® was not phototoxic. IR3535® caused mild eye irritation in the rabbit which was reversible and does not imply classification according to Directive 67/548/EC. Due to the stricter cut-off values in the CLP-Regulation (EC) No 1272/2008, IR3535® should be classified as an eye irritant (Category 2). Respiratory irritation was observed at a high dose in the acute inhalation toxicity study in the rat. However, apart from the bloody discharge at the nose only irregular respiration without any gross pathology on the respiratory tract was observed. As IR3535® is not a skin irritant, has no further classification regarding inhalation toxicity, and no respiratory irritation was reported in humans, the overall evaluation of the available data suggests that classification of IR3535® as a respiratory irritant R37 is not justified. Nevertheless, recommendations on ventilation or avoiding breathing in spray should be included in the product labels of spray formulations. Studies in guinea pigs showed that there is no indication that IR3535® has a potential to induce skin sensitisation, nor has a potential to induce photoallergenicity. In addition, there is no data available (human data e.g. market surveillance data, animal studies, open literature) which may be indicative of the potential of IR3535® to cause skin and respiratory irritation, or skin sensitisation and sensitisation by inhalation in humans.

Short- and Medium-term toxicity

The oral repeated toxicity of IR3535® was studied in a 28-day oral toxicity study in the rat, dog, and rabbit, and a 90-day oral toxicity study in the dog. Apart form the higher incidence of gastrointestinal symptoms at 500 mg and 1000 mg/kg bw/d in the dog, and the deepened breathing and unrest after administration of 1500 mg/kg bw/d in the rabbit, the oral administration of IR3535® was well tolerated. The occurrence of vomiting in the dog without evidence of any physiological alternations was considered a spontaneous and local reaction due to the foul palatability of IR3535®. In the rat (28-d) and dog studies (28-d, 90-d) no evidence of systemic toxicity was found up to and including the highest doses tested (dog, 90-d: 1000 mg/kg bw/d). However, in the 28-d rabbit study a systemic NOAEL after repeated oral administration was established at 500 mg/kg bw/d based on decreased bw (gain) and food consumption at 1500 mg/kg bw/d.

The dermal repeated toxicity of IR3535® was studied in a 28-day dermal toxicity study in the rabbit and a 90-day dermal toxicity study in the rat. In the rabbit, the administration of IR3535® in aqueous methyl hydroxyethyl cellulosegel P300 caused minor irritant effects (oedema and erythema) at the application site which was confirmed by histopathological

findings (local NOAEL 33.3 mg/kg bw/d). However, no local effects were observed up to a dose level of 3000 mg IR3535®/kg bw/d administered in a cream formulation in the rat (although dose-dependent minor irritant effects were observed in the rat 28-d dermal toxicokinetic range finding study). No substantial systemic effects were observed in both studies up to and including the highest doses tested (rabbit, 28-d: 333.3 mg/kg bw/d; rat, 90-d: 3000 mg/kg bw/d).

The inhalation repeated toxicity of IR3535® was not investigated.

Long-term toxicity

The chronic toxicity of IR3535® was not investigated.

Genotoxicity

In vitro, IR3535® was not mutagenic in bacterial and mammalian cells up to and including the limit concentration of 5000 µg/plate or 5000 µg/mL, respectively. In V79 cells, IR3535® was clastogenic in the absence of S9-mix at a concentration of 5000 µg/mL. In contrast, in CHO cells, IR3535® was clastogenic in the presence of metabolic activation at cytotoxic concentrations of 4000 and 5000 µg/mL only, indicating that clastogenicity observed may be the result of cytotoxicity. Therefore, results of the in vitro cytogenicity experiments are considered to be equivocal. *In vivo*, IR3535® did not induce micronuclei in mice bone marrow up to and including the MTD. The absence of mutagenicity in vivo was also observed in a chromosome aberration test in bone marrow in rats. It was shown in appropriate experiments that IR3535® reaches the target tissue i.e. the bone marrow in high concentrations. The overall evaluation of the complete genotoxicity data leads to the conclusion that IR3535® has no genotoxic potential.

Carcinogenicity

The carcinogenicity of IR3535® has not been investigated. However, (*i*) the overall genotoxicity data indicates that IR3535® has no genotoxic potential; (*ii*) the chemical structure of IR3535® shows no similarity to any known carcinogen or mutagen; (*iii*) no significant findings were noted for IR3535® in the 90-day studies in rats and dogs, i.e. no organ toxicity and no evidence for chronic tissue damage has been observed even at very high systemic exposure levels; (*iv*) no adverse effects to IR3535® have been reported over the last 20 years of experience in the European market. Hence, it can be concluded that there are no indications that IR3535® has any potential for carcinogenicity.

Reproductive and developmental toxicity

The reproductive toxicity of IR3535® was studied in a two-generation study in the rat. The developmental toxicity of IR3535® was studied in rabbit and rat teratogenicity studies.

The two-generation study involving gavage administration of IR3535® in the rat showed that IR3535® exerts no effect on the different reproduction parameters examined and induces no malformations in the selected dose range. The NOAEL for parental toxicity was considered to be 300 mg/kg bw/d based on mortalities at the next higher dose, 1000 mg/kg bw/d. $NOAEL_{parental}$ = 300 mg/kg bw/d; $NOAEL_{offspring}$ = 1000 mg/kg bw/d; $NOAEL_{reproduction\ parameters}$ = 1000 mg/kg bw/d.

The teratogenicity studies involving gavage administration of IR3535® in the rabbit and in the rat showed that IR3535® exerts no foetotoxic or teratogenic effects. No treatment-related effects were noted on the type and incidence of malformations and developmental variations in the selected dose range. In the rabbit, IR3535® caused maternal toxicity (decreased food consumption, body weight gain) during the first 3 days of dosing at 600 mg/kg bw/d. IR3535® is not considered toxic to development. $NOAEL_{marternal}$ = 300 mg/kg bw/d; $NOAEL_{developmental}$ = 600 mg/kg bw/d.

Neurotoxicity

The neurotoxic potential of IR3535® has not been investigated. However, there were no indications for a neurotoxic potential of IR3535® in the acute, subacute, subchronic, and reproduction toxicity studies. Moreover, the structural formula of IR3535® does not belong to groups / classes of chemicals known to be neurotoxic. It can be assumed that IR3535® does not have a neurotoxic potential.

2.2.1.1.2 Hazard identification of the Biocidal Model Formulation

Percutaneous absorption

For water/ethanol-based 20 % IR3535® market formulations a dermal penetration of 14 % was determined for a 12 hour exposure (~ typical use condition of 10 hours) based on the outcome of the human volunteer study. Based on the findings of this study, a dermal absorption of 14 % is also valid for an exposure of 24 hours. The water/ethanol-based 20 % IR3535® market spray formulation used in this volunteer study represents a worst case formulation with regard to skin penetration (main component is ethanol, and in addition contains other well known enhancers of skin penetrating properties of substances). Therefore, a dermal absorption of 14 % derived from this study is also relevant for 20 % IR3535® lotion/cream formulations.

Acute toxicity

The water/ethanol-based spray-pump 20 % IR3535® market formulation is of low toxicity via the dermal route when tested in the rat. No systemic effects/mortalities were noted. Local effects were characterised by slight erythema. Very slight erythema persisted to study termination. There were slight signs of abnormal excretion and discoloured areas.

Irritation and sensitization

In rabbits and human volunteers, the water/ethanol-based 20 % IR3535® model formulation did not produce dermal irritation. In rabbits the formulation caused very slight erythema that persisted until day 14. The slight edema was reversible. Nevertheless, the skin reactions observed did not trigger classification/labelling. The human volunteer study performed with the same spray formulation did not report any adverse findings or signs of dermal and respiratory irritation. Moreover, there are no indications for skin irritation potential of market formulations of up to 20 % IR3535® for more than 30 years of human experience (European market surveillance data, Pubmed search, personal communication Prof. A Goossens K.U.Leuven). The mild responses observed in rabbits are considered of low relevance to human risk. Thewater/ethanol-based 20 % IR3535® formulation caused positive corneal and conjunctival eye irritation in the rabbit. The formulation is considered an eye irritant. Studies in guinea pigs showed that there is no indication that the water/ethanol-based pump-spray 20 % IR3535® model formulation has a potential to induce skin sensitisation. In addition, there is no data available for more than 30 years of human experience (human data e.g. market surveillance data, animal studies, open literature) which may be indicative of the potential of the water/ethanol-based pump-spray 20 % IR3535® model formulation to cause skin and respiratory irritation, skin sensitisation and sensitisation by inhalation in humans.

2.2.1.2 Effects Assessment, AEL Setting

2.2.1.2.1 Systemic AELs

The critical endpoints of IR3535® in the toxicological studies are identified as reduced body weight and body weight gain, as well as reduced food consumption. The NOAELs have been derived from the studies in the most sensitive species showing these effects: the rabbit. It is suggested to consider these effects in the risk assessment.

POD Acute and Medium-term

No 90-days dermal toxicity study was performed in the most sensitive species, the rabbit. Additionally, in the 28-days dermal toxicity study in the rabbit the highest dose was set too low (333.3 mg/kg bw/d, only 100 mg/kg bw/d systemically). Although human exposure is mainly dermal, the PODs are based on oral studies.

1. NOAEL IR3535®, oral, developmental, rabbit = 300 mg/kg bw/d (based on decreased food consumption and bw gain during the first 3 days of dosing at 600 mg/kg bw/d)

2. NOAEL IR3535®, oral, 28-days, rabbit = 500 mg/kg bw/d (based on decreased food consumption during the first half of the study in males, and decreased bw (gain) in both sexes at 1500 mg/kg bw/d)

Different dose spacing in these studies resulted in different NOAELs and LOAELs. As the NOAEL of the developmental study was based on marginal maternal toxicity observed at 600 mg/kg bw/d, it is considered that the most plausible NOAEL is closely below this value. Therefore, the overall, combined NOAEL which has been considered for risk assessment and used as the POD is a NOAEL = 500 mg/kg bw/d.

POD Long-term

No long-term toxicity studies are available for the most sensitive species: the rabbit.

A 2-generation study available for the rat revealed a NOAEL of 300 mg/kg bw/d. The only, but very, adverse effect observed was mortality at the next higher dose, 1000 mg/kg bw/d (highest dose tested). The mortality could not be ascribed to another reason than treatment and, as such, was considered treatment-related. No other dose in between these doses was tested. Due to bad dose-spacing the RMS BE is of the opinion that the real NOAEL is higher. In the 90-day dermal study in rats no toxicity was observed (NOAEL: 3000 mg/kg bw/d).

The RMS BE preferred to use the most reliable data from the most sensitive species, the rabbit (the teratogenicity study, the 28-day oral study), without an additional AF for duration.

Acute NOAEL = 500 mg/kg bw/d (rabbit, overall, developmental study/28-d study)

Medium-term NOAEL = 500 mg/kg bw/d (rabbit, overall, developmental study/28-d study)

Long-term NOAEL = 500 mg/kg bw/d (rabbit, overall, developmental study/28-d study)

As there is no indication for route-specific differences in toxicity (not reflected by absorption data) and as IR3535® did only elicit minor local effects in experimental animals, there is no hindrance for the use of an AEL derived from a NOAEL based on studies using the oral route of administration, i.e. setting the level of internal exposure that is toxicological acceptable.

Assessment factors: default 100-fold (10x10)
Oral absorption: 100 %

In conclusion:	**Acute AEL**	=	**5**	**mg/kg bw/d**
	Medium-term AEL	=	**5**	**mg/kg bw/d**
	Long-term AEL	=	**5**	**mg/kg bw/d**

2.2.1.2.2 Local AECs

Local dermal effects were observed in the 28-day dermal study in the rabbit (key study) and also in a 28-day dermal toxicokinetic range finding study in the rat.

According to the Guidance document "Risk Characterization of local effects" (EU, 05/03/2010) the effects observed are interpreted as minor irritant effects.

In the 28-day dermal toxicity study in rabbits, no local effects were observed in the group treated with a solution (vehicle: 1 % aqueous methyl hydroxyethyl cellulose gel 300P) containing 3.3 % IR3535®. The group treated with 10 % IR3535® showed stage 1 erythema (barely perceptible, mild), in a few cases increasing to stage 2 (pronounced), and edema starting at day 6 of treatment. 14 days after start of treatment the local effects reached a maximum, but then slowly receded and almost disappeared after 4 weeks of treatment (no edema, only 3 animals with stage 1 erythema). The reversibility could also be observed in the group treated with 33.3 % IR3535®: The erythema reached a maximum at day 10 (mainly stage 2) and then slowly receded up to the end of treatment. Beside erythema and edema no other skin alterations were observed. Corresponding histological findings consisting of round cell infiltrations in the upper third of the corium, acanthosis, hyperkeratosis and parakeratosis as displayed by squamous epithelium and leukocyte infiltration were also noted in the 10 % and 33.3 % IR3535® groups.

However, in the 90-day dermal study in rats, where the animals were treated with formulations containing 0, 2, 20 and 60 % IR3535® for 6 hours/day, under occlusive conditions, higher incidences of local effects were observed in the control and low dose groups than in the mid and high dose groups (Pfister et al., 1996, A6.4.2/01). Intergroup differences noted for incidence and duration of local reactions were not dose-related. In contrast with these findings, Arcelin and Stegehuis (1996, A6.2./05) reported in a 28-day rat dermal toxicokinetic range finding study (range finding study for the 90-day dermal toxicity study) very slight to slight patchy erythema and scaling incidences with persistence and severity being dose-dependent. LOELlocal = 100 mg/kg bw/d = 2 % IR3535® in cream.

For risk characterisation of local effects:

It must be taken into account, that testing in rabbits in general overpredicts skin effects in humans (Jirova et al., 2010, Contact Dermatitis 62, 109-116). This is also observed with IR3535®: In a modified Duhring chamber test, a solution containing 10 % IR3535® was tested in 10 volunteers for 5 days under occlusive conditions. No local effects were observed, all scores were 0 (Blitz 1996, A6.1.4/04). The applicant submitted another study (2010-04-13), with repeated application of formulations containing 15 % IR3535® to humans once or twice a day for three consecutive weeks, which resulted in no local effects (Hopf, 1979: very poorly reported and can not be used for further assessment according to the RMS BE). Moreover, since IR3535® has been formulated for more than 30 years in products at concentrations of up to 20 % and no complaints are known from the market it is concluded that IR3535® is without any evidence for local intolerance for consumers after dermal application.

In addition, only mild erythema without oedema was observed in acute dermal toxicity studies performed with high doses (6.35 to 10.00 g/kg bw for 6 hours of undiluted IR3535®) in the dog, rat and mouse which was completely reversible (healed within 72 hrs) (Leushner, 1973 and 1981). In the acute dermal toxicity study performed with the water/ethanol-based spray-pump 20 % IR3535® market formulation (rat, limit test, 5 g/ kg bw for 24 hours) local effects were characterised by slight erythema (Hurley, 2006).

Considering that (i) the effects observed in rabbits treated topically with different concentrations of IR3535® for 28 days were reversible during treatment suggesting no cumulative effects, (ii) IR3535® appeared to induce an inverse dose-response relationship on

the skin of rats during a subchronic dermal toxicity study (lowest incidence of local findings in the mid and high dose group), (iii) the rabbit is more sensitive than humans with regard to skin irritation, (iv) tests with volunteers revealed no irritating effects of formulations containing IR3535® , and (v) clinical absence of lesions in a period of 30 years (European market surveillance data; pubmed search; personal communication, Prof. A. Goossens, K.U.Leuven), it seems justified to consider the mild and reversible responses in rabbits of low relevance to human risk. It is concluded that a risk characterisation for local effects of IR3535® is not justified and the derivation of a local AEC is not needed.

2.2.1.3 Exposure assessment

IR3535®-based formulations belong to Product Type 19 "Repellents and Attractants" Subtype 01 "Repellents and Attractants applied directly on human or animal skin" according to the first review regulation of the BPD (Commission Regulation 1896/2000). Formulations containing IR3535® on the market are pump-sprays and lotions.

Products are applied against insects occurring outdoor, during summer time (period of 28 days)

- The products are sold as consumer products: use for adults and children
- No professional use

IR3535® formulations are applied directly to intact skin of adults and children. Only the following exposed body parts (i.e. skin not covered by clothes) are to be treated: face, arms; legs and also for adults the hands; the trigger spray product is not to be sprayed directly on the face. IR3535® formulations must not be applied to children's hands'.

The trunk is not treated with IR3535® containing formulations. At TM November 2010, it was agreed to add the word "ONLY" in the label specifying the parts of the body where the product should be applied: "ONLY apply to face, hands, arms, and legs"

The exposure and risk assessments are performed on the basis of a model formulation (dummy product), which contains IR3535® as the only active substance. The model formulation was developed on the basis of water and ethanol. The concentration of IR3535® in the model formulation is comparable to IR3535® concentrations in products currently on the market in the EU (a concentration of 20 % w/w is used).

Thus, exposure to IR3535® takes place via dermal exposure for pump-sprays and lotions (primary exposure). Inhalation exposure is also possible resulting from respiring aerosols after spraying. The fraction of particles smaller than 5 µm was shown to be below 0.6 % for the tested IR3535®-based formulation. Hence, the respirable fraction is below 0.3 % and therefore it is assumed that the other 99.7 % precipitate in the upper airways and are taken in orally. Secondary exposure is possible for adults treating or handling children. Hand to mouth transfer might be possible for small children. However this scenario is not considered to be a significant route of exposure because of bad palatability (bitterness) preventing repeated mouthing by small children and you may not apply to children's hand.

The estimation of exposures follows the recommendations of the Technical Notes for Guidance (TNsG), Human Exposure to Biocidal Products (2002) as revised by User Guidance version 2 (April 2007), TGD and values from RIVM reports.

The total internal dose is calculated with values for inhalative absorption of 100 %, for oral absorption of 100 %, and for dermal absorption of 14 %.

Human exposure to IR3535® via food is not considered to be relevant because IR3535® is not used for and/or during food production, or in rooms where food is produced, processed or stored. This is also the case for feeding stuffs.

2.2.1.3.1 INDUSTRIAL EXPOSURE: Production/Formulation of active substance

Production: the whole reaction process (including loading of raw materials) is carried out in a closed device. All substances related occupational limit concentrations are far below critical data defined by legal regulations (MAK1 / TRK2 values). Potential human exposure is only possible during loading and cleaning/service processes. All handling with respect to these processes are carried out using personal protection measures, which are related to the respective task (up to full personal protection for special cleaning and service tasks).

IR3535®, the active substance (ethyl butylacetylaminopropionate), is produced in a closed process. The process of production is described in the confidential annex

Formulation: No information on exposure was considered necessary to provide exposure data for the formulation of biocidal products as Merck is neither producing, nor placing on the market IR3535® based biocidal products. Therefore, a model formulation was defined for the purpose of the product dossier, which is only produced in extremely small amounts for study purposes. However, in modern formulation plants typically automated equipment is used to add the formulation ingredients and to fill the formulated product into the respective vessels (closed systems). The workers (trained professionals) usually wear personal protective equipment (e.g. gloves). The exposure during the formulation task should be negligible.

2.2.1.3.2 NON-PROFESSIONAL EXPOSURE from the use of the biocidal product

The human health risk assessment for IR3535® is performed on the basis of a spray and a body lotion application. About 168 mL product containing 20 % IR3535® is used per adult person per year.

Exposure during these applications has been taken into account for the dermal route and for inhalative exposure to the aerosol by spray application. However, it has been shown that inhalative exposure to the aerosol is negligible due to the small fraction of respirable particles.

Oral exposure is not considered to be relevant.

Table 2.2.1.3-1 Summary Non-professional exposure biocidal use

Intended use (PT)	Category of population	Exposure scenario	a.s* [%]	Dermal Estimated internal exposure [mg/kg bw/day]	Inhalation Estimated internal exposure [mg/kg bw/day]	Oral Estimated internal exposure [mg/kg bw/day]
PT19 (Insect repellent)	Adult	Spray and lotion application 2 applications/day	20 %	2.80	0.000018	0.00582
	Children (9-10 years)	Spray and lotion application 2 applications/day	20 %	4.22	0.000018	0.00609
	Small Children (3.5 years)	Spray and lotion application 1 applicaton/day	20 %	2.62	0.000016	0.00521
	Infant (1 year)	Spray and lotion application 1 applicaton/day	20%	2.98	0.000018	0.00602
	Infant (10.5 months)	Spray and lotion application 1 applicaton/day	20%	3.09	0.000019	0.00626
	Infant (3 months)	Spray and lotion application 1 applicaton/day	20%	3.66	0.000022	0.00737

* Concentration of active substance in the treatment solution

2.2.1.3.3 INDIRECT EXPOSURE as a Result of Use (Secondary Exposure)

Hand to mouth transfer for small children has been developed consistently with the DEET dossier.

A parent applying (spraying) the product on children and herself/himself has been taken into account as well.

Inhalation of volatilized residues after application is relevant. The exposure to volatilised residues indoors was calculated under the provisions of the example calculation in the TNsG on Human exposure, part 3, page 50. It was assumed that the airborne concentration of IR3535® will not exceed 1 % of the saturated vapour concentration (SVC).

Table 2.2.1.3-2 Summary Indirect exposure as a result of use

Secondary exposure scenario	Calculated exposure to IR3535®	
Hand-mouth transfer reverse reference scenario (oral exposure)	Adult	up to 12.5 applications a day
	Child (9-10 y)	up to 3.3 applications a day
	Small child (3.5 y)	up to 2.7 applications a day
	Infant (1 y)	up to 2.3 applications a day
	Infant (10.5 m)	up to 2.3 applications a day

	Infant (3 m)	up to 1.9 applications a day
Parent treating two children and himself/herself (spraying) (combined inhalative and oral exposure)	Adult:	0.0175 mg/kg bw/day
Inhalation of volatilised residues after application (inhalative exposure)	Adult: Child (9-10 y): Small child (3.5 y): Infant (1 y): Infant (10.5 m): Infant (3 m):	0.027 mg/kg bw/day 0.028 mg/kg bw/day 0.048 mg/kg bw/day 0.057 mg/kg bw/day 0.058 mg/kg bw/day 0.069 mg/kg bw/day

2.2.1.4 Risk characterisation

The risk characterisation is in general based on the assumption that the products are used according to the conditions for normal use.

2.2.1.4.1 Industrial Workers in production/formulation

There is no concern for industrial workers in the production and formulation of the active substance.

2.2.1.4.2 Human health risk for non professional users (Primary exposure)

Table 2.2.1.4-1 Non-professional users PT19 – Primary Exposure

Exposure assessment Spray/lotion application		Estimated Internal Exposure (mg/kg bw/d)				Relevant NOAEL LOAEL [mg/kg.bw day] - Reference Value	AF MOE_{ref}	MOE	Exposure /AEL
		inhalation uptake	oral uptake	dermal uptake	total uptake				
Tier 1	Adult (2 appl.)	0.000018	0.00582	2.80	2.81	NOAEL 500 mg/kg bw/d $AEL_{medium\ term}$ 5 mg/kg bw/d	100	178	0.56
	Child (9-10 y) (2 appl.)	0.000018	0.00609	4.22	4.22		100	118	0.84
	Small child (3.5 y) (1 appl.)	0.000016	0.00521	2.62	2.63		100	190	0.53
	Infant (1 y) (1 appl.)	0.000018	0.00602	2.98	2.99		100	167	0.60
	Infant (10.5 m) (1 appl.)	0.000019	0.00626	3.09	3.09		100	162	0.62
	Infant (3 m) (1 appl.)	0.000022	0.00737	3.66	3.66		100	136	0.73

Conclusion: There is no concern for adults and children using the biocidal product (spray/lotion formulation containing 20 % IR3535®) as a Repellent Subtype PT19.01, when used twice a day.

For small children and infants the use should be restricted to 1 application a day. Initially, the applicant chose to not support use on children younger than 1 year of age as a precautionary

measure, reasoning that several physiological functions are not yet fully developed in infants. However, as the exposure assessment for infants below 1 year of age is acceptable and as there might be a need for repellents that can be used on infants in regions where vector diseases are present, complete exclusion for use on children below 1 year of age is not fully justified. Nevertheless, caution must still be taken when using these products on infants and it is rather recommended to use physical protection such as mosquito nets and/or to use products very responsibly.

Apply the repellent only to exposed skin. Do not use under clothing. When using a pump spray, do not spray directly on face –spray on hands first and then apply to face. Do not allow children to handle the product. You may not apply to children's hands. The product can be applied indoors and outdoors. When the product is a spray and applied indoors, care should be taken to use in a well-ventilated room and to not breath in the spray.

2.2.1.4.3 Human health risk from indirect exposure as a result of use (Secondary exposure)

Table 2.2.1.4-2 Indirect Exposure PT19 – Secondary Exposure – Intended use

Exposure assessment	Estimated internal exposure [mg/kg bw/day]			Relevant NOAEL LOAEL [mg/kg bw/day] Reference value	AF MOE_{ref}	MOE	$\frac{Exposure}{AEL}$
	inhalation uptake	oral uptake	total uptake				
TIER 1 (Worst Case) – Intended use							
Adult treating 2 children and himself/herself	0.000053	0.01745	0.0175	NOAEL 500 mg/kg bw/d $AEL_{medium\ term}$ 5 mg/kg bw/d	100	28571	0.00
Inhalation of volatilised residues after application							

Adult	0.027	-	0.027	NOAEL 500 mg/kg bw/d	100	18519	0.01
Child (9-10 y)	0.028	-	0.028		100	17857	0.01
Small child(3.5 y)	0.048	-	0.048		100	10417	0.01
Infant (1 y)	0.057	-	0.057	$AEL_{medium\ term}$ 5 mg/kg bw/d	100	8772	0.01
Infant (10 m)	0.058	-	0.058		100	8621	0.01
Infant (3 m)	0.069	-	0.069		100	7246	0.02

Table 2.2.1.4-3 Indirect Exposure PT19 – Secondary Exposure – Unintended use

Exposure assessment	**# applications/day**
TIER 1 (Worst Case) – Unintended use	
Hand-mouth transfer (reverse reference scenario)	
Adult	up to 12.5 applications a day
Child (9-10 y)	up to 3.3 applications a day
Small child(3.5 y)	up to 2.7 applications a day
Infant (1 y)	up to 2.3 applications a day
Infant (10.5 m)	up to 2.3 applications a day
Infant (3 m)	up to 1.9 applications a day

Conclusion: There is no concern for indirect secondary exposure for adults, children and infants.

Overall conclusion:

The biocidal model formulation (pump spray, lotion) containing 20 % IR3535® is intended for use by the general public as a repellent applied directly on the human skin (PT19.01).

The overall outcome of the risk assessment for humans, that has covered normal use of the biocidal product together with a worst case scenario (only applied on face, arms, hands, legs, twice a day), is that proper use, i.e. use in compliance with the conditions on the label, of the model formulation containing 20 % IR3535® is considered safe for adults and children. Use on small children younger than 3.5 years should be restricted to one application a day, unless it can be demonstrated in the application for product authorisation that the product will meet the requirements without such measures.

Initially, the applicant chose to not support use on children younger than 1 year of age as a precautionary measure, reasoning that several physiological functions are not yet fully developed in infants. However, as the exposure assessment for infants below 1 year of age is acceptable and as there might be a need for repellents that can be used on infants in regions where vector diseases are present, complete exclusion for use on children below 1 year of age is not fully justified. Nevertheless, caution must still be taken when using these products on infants and it is rather recommended to use physical protection such as mosquito nets and/or to use products very responsibly.

As the biocidal product must not be applied on the trunk, additional labelling should include the phrase ‘only apply to arms, hands, legs, and face’.

However, it might be possible that at product authorisation stage products are marketed that can be used on the trunk as well. In this case, the human exposure assessment should take this extended use into account.

Furthermore, recommendation on ventilation or avoiding breathing in spray must be included in the product labels of spray formulations.

Products may not be applied to children’s hand.

Additionally, it has to be kept in mind that using a cream (e.g. suncream) on top of the applied repellent can enhance the dermal penetration of the repellent because of the occlusive conditions reacted.

2.2.2 Environmental Risk Assessment

2.2.2.1 Fate and distribution in the environment

IR3535® is used in insect repellents (PT19) that are applied on uncovered human skin. Products containing IR3535® will be used indoors and outdoors. However the main emission pathway to the environment is assumed to be indirect due to bathing and showering of treated people. Based on the physico-chemical properties it is expected that the emissions primarily will affect the aquatic compartment.

IR3535® is not ready biodegradable according to two screening tests, but in a Sewage Treatment Plant (STP) simulation test 99 % elimination was measured. In an aerobic water/sediment degradation study, IR3535® was shown to remain mainly in the water phase. There it was first rapidly degraded to its free acid, after which this metabolite ultimately degraded after a lag phase.

No photolysis was observed in water and hydrolysis only occurred slowly under alkaline conditions (DT_{50} = 176.5 h at 25 °C and pH 9 or 866.13 h at 12 °C). Under acidic and neutral conditions IR3535® is hydrolytically stable.

The vapour pressure of IR3535® is low (0.15 Pa at 20 °C) which results in low exposure to the atmosphere. The half-life of IR3535® in air was calculated to be about 0.5482 days or 13.16 hours due to reaction with OH-radicals (24-hr day). Thus accumulation of IR3535® in air and long range transport is unlikely.

IR3535® is a liquid at room temperature and the solubility in water is 70 g/L (at 20 °C). The log P_{ow} is 1.7 (at 23-24 °C) indicating that IR3535® has a low potential for bioaccumulation.

Based on the adsorption/desorption test a mean (arithmetic) K_{oc} form 475.25 L/kg was registered.

2.2.2.2 Effect assessment

No toxic effects where observed during the acute toxicity studies on fish (*Brachydanio rerio*), *Daphnia magna* and algae (*Desmodesmus subspicatus*) (LC_{50} >100 mg/L). Therefore IR3535® is considered as not toxic for the aquatic environment.

The effect on aerobic biological sewage treatment processes was assessed by determining inhibition of respiration of the micro-organisms present in activated sludge following 3 hours contact. No inhibitory effect on aquatic microbial activity was registered for IR3535® (EC_{50} > 1000 mg/L).

Long term aquatic tests were not required because no acute toxicity was observed for the aquatic environment and the substance is primarily emitted to the STP before reaching the aquatic environment. Besides the Sewage Treatment Plant (STP) simulation test showed an elimination of 99 % in the STP.

No marine species were tested based on the presence of studies performed on freshwater species, all suggesting low toxicity and because no major emissions to the marine environment are expected.

In the absence of any long-term toxicity endpoints and marine data, the TGD on Risk Assessment prescribes an assessment factor of 1000 for the freshwater environment and 10000 for the marine environment.

For the sediment compartment, there are also no toxicity data available. The $PNEC_{sediment}$ was calculated based on equilibrium partitioning method and $PNEC_{water}$.

No terrestrial toxicity tests were performed for IR3535®. Due to the method of application directly on the skin only limited and very local emissions to the soil are expected. IR3535® is not likely to become accumulated in the soil in large amounts. $PNEC_{soil}$ has been calculated based on the equilibrium partitioning method.

The physicochemical properties of IR3535® do not suggest that this substance will pose a risk to the atmospheric environment. Therefore no PNECs where calculated for this compartment.

The low BCF values suggest that IR3535® has a low bioaccumulation potential. Therefore the risk of secondary poisoning via ingestion of contaminated food (eg. earthworms or fish) by birds or mammals is also low and no avian dietary tests were required.

2.2.2.3 PBT assessment

Due to the failing of the ready biodegradability screening tests, IR3535® could initially be classified as a potentially persistent substance. However, an STP-simulation test showed elimination up to 99 % after 28 days, indicating that IR3535® is biodegradable.

The DT_{50} (12 °C) of IR3535® in water/sediment degradation study ranged from 12.88 to 15.95 days in water, which is well below the P-criterion of 40 days. IR3535® remained in the water phase, so no half-life for the sediment can be determined. During the water/sediment degradation study, IR3535® rapidly degraded to its free-acid. The degradation of this free acid knows two phases, a lag phase and a rapid, ultimate biodegradation phase. During the lag phase, slow degradation of this free acid was observed. Through kinetic analysis, DT_{50}'s (12 °C) ranging between 163.29 and 208.61 days in water and 149.25 and 367.92 days in sediment could be determined. Solely based on this phase, the IR3535-free acid could be classified as persistent and even very persistent. However, after this lag phase, the IR3535-free acid very rapidly degrades, with determined DT_{50}'s (12 °C) ranging between 8.48 and 10.77 days in water and 5.40 and 7.11 days in sediment. Solely based on this phase, the IR3535-free acid should not be classified as persistent. For the evaluation of the P-criterion, the degradation rates of the two phases must be combined. Based on the overall DT_{50}-values which are based on the remaining amounts of IR3535-free acid at the end of the water/sediment study, IR3535-free acid should not be classified as persistent.

No degradation studies in soil are available for IR3535®.

The BCF calculated through a QSAR with the input of the log P_{ow} was 5.6. This value is well below the B-criterion of 2000.

The toxicity criterion is based on chronic toxicity data. For IR3535®, no such data is available.

The algae growth inhibition test was performed under a nominal concentration of 0.1g/L. After 72 hours no effects were observed, so it could be said that the NOEC is larger than 0.1g/L. This NOEC value is much larger than the T-criterion value of <0.01 mg/L.

IR3535® is not carcinogenic, mutagenic or teratogenic. No indication or data for IR3535® are available that indicate potential endocrine disruptive properties.

Conclusion: IR3535® does not meet any of the criteria for Persistent, Bioaccumulative and Toxic (PBT) substances or the very Persistent, very Bioaccumulative (vPvB) category.

2.2.2.4 Exposure assessment and risk characterisation

The risks for the environment are characterized by comparing the toxicity of the substance (PNECs) with the exposure estimates (PECs)

Possible environmental emissions were calculated for the indoor application of IR3535® formulations through a dummy product containing 20 % active substance. These emissions only occur indirectly, through wash-off during bathing and showering. Because so far, no emission scenario has been developed for PT19.01 – repellents, the ESD for product type 1 (human hygiene products) was used. This was justified through the similar use and manner of application of repellents.

The ESD for PT1 offers two scenarios, one based on estimated yearly tonnage and one based on average daily consumption. Emissions through both scenarios were calculated and the worst case emission – in this instance the average daily consumption scenario – was used during the rest of the risk assessment.

No emissions were calculated for possible outdoor scenarios (e.g. direct emission to surface waters through swimming). This was agreed upon during the TM IV 2010, because no general scenario had yet been agreed upon. However, during product authorization stage, this emission route must be taken into account.

In a tier one assessment, no biodegradation was taken into account while calculating the PECs. In a tier two assessment, the STP simulation test was used to model 99 % elimination in the STP.

For the aquatic compartment and the soil all the calculated PEC/PNEC ratios are below 1, both for the tier 1 and the tier 2 assessment.

For the groundwater, an initial risk was calculated through the tier 1 assessment. However, in the tier 2 assessment no further risks are expected, because the possible emissions to soil and groundwater are negligible due to the large elimination in the STP.

In conclusion of the environmental risk assessment, it is expected that the risks to non target organisms from the use of IR3535® in insect repellents are low, even if adopting a conservative (realistic worst case) scenario for the PEC calculations. None of the PEC/PNEC ratios exceed 1 when taking elimination in the STP into account.

2.2.3 Overall conclusions of the evaluation

Table 2.2.3-1 Overall summary

Scenario	Efficacy	Human primary exposure			Human secondary exposure		Environment: indoor scenario				Environment: outdoor scenario
		adult	child 9-10 y	child 3.5 y infant 1 y 10.5 m 3 m	adult	child 9-10 y 3.5 y infant 1 y 10.5 m 3 m	STP	Aquatic Com-part-ment	Ter-res trial Com-part-ment	Atmos-phere	
Dummy 20 % a.s. Spray & lotion applications **2 applications/day**	Basic efficacy demonstrated for a.s. Full/ robust efficacy studies for all claimed target organisms for IR3535®-based formulations are required at the Product Authorisation Stage.	+	+	-	+	+	+	+	+[1]	+	To be assessed at Product Authorisation Stage
Dummy 20 % a.s. Spray & lotion applications **1 applications/day**		+	+	+	+	+	+	+	+	+	

+ No unacceptable risks were identified
+[1] Risk for groundwater identified for first tier assessment, but reduced to 0 for 2nd tier assessment

2.2.4 Listing of endpoints

In order to facilitate the work of Member States in granting or reviewing authorisations, the most important endpoints, as identified during the evaluation process, are listed in appendix I.

3 DECISION

3.1 BACKGROUND TO THE PROPOSED DECISION

Ethyl butylacetylaminopropionate (know as well under the name IR3535®) is intended to be used in formulations as an insect repellent to be applied directly to human skin. Formulations containing Ethyl butylacetylaminopropionateare only intended by the applicant to be used by non-professionals.

The physico-chemical properties of Ethyl butylacetylaminopropionateare considered acceptable. Ethyl butylacetylaminopropionateis not is not explosive, not highly flammable and is stable at room temperature.

Ethyl butylacetylaminopropionatewas shown to be efficacious against mosquitoes (*Anopheles sp., Aedes sp., Culex sp.*), sand flies (*Phlebotomus sp.*), ticks (*Ixodes sp.*), lice (*Pediculus sp.*), flies (*Stomoxys sp.*), wasps (*Pollistes sp.*) and bees (*Apis sp.*). At product authorisation stage, full robust study summaries of the particular formulations and claimed target organisms will be required.

In regard to the human health exposure and effects, based on the risk assessment conducted of an formulation containing 20 % active ingredient, safe use has been demonstrated for the intended use of 2 applications per day for adults and children older than 9 years of age. For children of 3.5 years and younger, use had to be restricted to only 1 application per day to be able to indicate a safe use. Thus, products intended for application on human skin should be restricted in use when using on children of 3.5 years and younger, unless it can be demonstrated in the application for product authorisation that the product will meet the requirements without such measures.

Initially, the applicant chose to not support use on children younger than 1 year of age as a precautionary measure, reasoning that several physiological functions are not yet fully developed in infants. However, as the exposure assessment for infants below 1 year of age is acceptable and as there might be a need for repellents that can be used on infants in regions where vector diseases are present, complete exclusion for use on children below 1 year of age is not fully justified. Nevertheless, caution must still be taken when using these products on infants and it is rather recommended to use physical protection such as mosquito nets and/or to use products very responsibly.

The environmental risk assessment limited itself to an assessment of the emissions as a consequence of washing treated skin, resulting in indirect exposure to the STP and surface

water. No direct emissions for possible outdoor scenario's (e.g. direct emission through swimming) have been considered, as no standardized scenario was available at the time this substance was evaluated. During product authorisation stage, this emission route should be considered.

For the environmental emission route considered, it is expected that the risks to non-target organisms from the use of ethyl butylacetylaminopropionatein insect repellents are low, even if adopting a conservative (realistic worst case) scenario for the PEC calculations. None of the PEC/PNEC ratios exceed 1 when taking elimination in the STP into account.

In conclusion, assessed from the documentation on the active substance ethyl butylacetylaminopropionate and the presented model formulation containing 20 % IR3535® the proposed manner and areas of use of products intended as repellents may be sufficiently effective for these uses without unacceptable risk neither to human health nor the environment

3.2 PROPOSED DECISION

The overall conclusion from the evaluation of ethyl butylacetylaminopropionate for use in product type 19 (Repellents and attractants) is that it may be possible for Member States to issue authorisations of products containing ethyl butylacetylaminopropionate in accordance with the conditions laid down in Article 5(1) b), c) and d) of Directive 98/8/EC.

It is therefore proposed to approve ethyl butylacetylaminopropionate as an active substance for use in product-type 19 (repellents and attractants), subject to the following specific conditions:

The active substance ethyl butylacetylaminopropionate shall have a minimum purity of 99 % w/w

The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by an application for authorisation, but not addressed in the Union level risk assessment of the active substance.

Authorisations are subject to the following condition:

> Primary exposure of humans to the product shall be minimized by considering and applying appropriate risk mitigation measures, including, where applicable, instructions on the amount and the frequency with which the product may be applied to on human skin;

3.3 ELEMENTS TO BE TAKEN INTO ACCOUNT WHEN AUTHORISING PRODUCTS

- An analytical method for the detection and identification of ethyl butylacetylaminopropionate in formulations was not submitted, because the formulation

described in this CAR is a model formulation and not specific. This point should be addressed in the national registrations for the specific formulations.

- Full robust efficacy studies for all claimed target organisms for formulations are required at the Product Authorisation Stage.

- Recommendation on ventilation or avoiding breathing in spray must be included in the product labels of spray formulations.

- Based on the available data and considerations, the non-submission of a short-term/subchronic/chronic inhalation toxicity study is currently considered justified. However, at the national product authorisation level authorities have to be alert for new formulations applied via spray with smaller droplet sizes.

- For this CAR a dermal penetration of 14 % was determined, based on a human volunteer study on the dermal penetration of a water/ethanol based pump-spray containing 20 % IR3535. The spray formulation used in this study was considered to represent a worst case formulation with regard to skin penetration, as the main component is ethanol and in addition contains other well-known skin penetration enhancers. Where at the product authorisation stage product specific data is not available and the 14% value is proposed by the applicant, the suitability of such a value should be assessed according to the available guidance on dermal absorption assessment for the authorisation of biocidal products.

  Possible enhanced dermal absorption due to simultaneous application of products other than the biocidal product in question (e.g. sunscreen lotion) should be considered when assessing products.

- The biocidal product assessed in this CAR must not be applied on the trunk and contains the additional labelling 'ONLY apply to arms, hands, legs, and face'. However, it might be possible that at product authorisation stage products are marketed that can be used on the trunk as well. In this case, the human exposure assessment should take this extended use into account.

- No particular concern for the use on children was identified during the risk assessment on human health, but when authorising products for use on human skin it is nevertheless appropriate that, following evaluation of the product, evaluating competent authorities consider whether additional specific restrictions or a recommendation to use physical protection alternatives should be required on the product label.

- Products must not be applied to children's hands.

- Direct emissions to surface water by swimmers should be kept in mind and assessed when authorizing products.

3.4 REQUIREMENT FOR FURTHER INFORMATION

It is considered that the evaluation has shown that sufficient data have been provided to verify the outcome and conclusions, and permit the proposal for the approval of ethyl butylacetylaminopropionate in accordance with Article 9 of Regulation (EU) No 528/2012.

3.5 UPDATING THIS ASSESSMENT REPORT

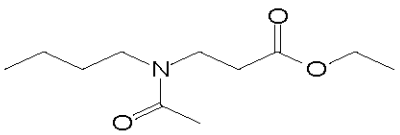
This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information submitted in relation with Regulation (EU) No 528/2012. Such adaptations will be examined and finalised in connection with any amendment of the conditions fort the approval of ethyl butylacetylaminopropionate.

APPENDIX 1: LISTING OF END POINTS

Chapter 1: Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labelling

Active substance (Common Name)	IR3535®, Ethyl butylacetylaminopropionate, ethyl N-acetyl-N-butyl-β-alaninate (EINECS)
Function	Insect Repellent
Rapporteur Member State	Belgium

Identity (Annex IIA, point II.)

Chemical name (IUPAC)	ethyl 3-[N-acetyl-N-butyl] aminopropionate
Chemical name (CA)	beta-alanine, N-acetyl-N-butyl-, ethyl ester
CAS No	52304-36-6
EC No	257-835-0
Other substance No.	CIPAC No.: 667
Minimum purity of the active substance as manufactured (g/kg or g/l)	≥ 990 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	none
Molecular formula	$C_{11}H_{21}NO_3$
Molecular mass	215.29 g/mol
Structural formula	

Physical and chemical properties (Annex IIA, point III)

Melting point	Test substance is liquid at room temperature (melting point < -90 °C) Purity : not indicated	
Boiling point	Endothermic effects slightly below 300 °C (metastable boiling point) purity: 99.8 %	
Temperature of decomposition	Exothermic effect at ca 141 °C (probably decomposition)	
Appearance	Clear colourless liquid (purity: 99.8 %)	
Relative density	0.998 (at 20 °C +/- 0.5 °C) (purity: 99.8 %)	
Surface tension	59.6mN/m at 20.0 °C	
Vapour pressure	0.15 ± 0.01 Pa at 20 °C (purity: 99.8 %)	
Henry's law constant	4.613 x 10^{-4} Pa m^3 mol^{-1} (20 °C)	
Solubility in water	70 g/L at 20.0 °C (in non buffered water) pH 5: 69.92 g/L at 20 °C (+/- 1 °C) pH 7: 56.72 g/L at 20 °C (+/- 1 °C) pH 9: 68.0 g/L at 20 °C (+/- 1 °C)	
Solubility in organic solvents (in g/l or mg/l, state temperature)	Acetone Ethyl acetate Dichloromethane n-Heptane Methanol p-Xylene (at room temperature)	> 250 g/L
Stability in organic solvents used in biocidal products including relevant breakdown products	Stable in common organic solvents	
Partition coefficient (log P_{ow})	log Pow : 1.7 (at: 23-24 °C) (HPLC method) log Pow : 1.5 (QSAR estimation by KOWIN v1.67)	
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH 4: > 365 days (50 °C) pH 7: > 365 days (50 °C) pH 9: 97,6 hours (30 °C) pH 9: 34,5 hours (40 °C) pH 9: 11,6 hours (50 °C)	
Dissociation constant	Not applicable, non-ionic substance	
UV/VIS absorption (max.)	No absorbance maxima (220 – 900 nm)	
Photostability (DT_{50}) (aqueous, sunlight, state pH) (point VII.7.6.2.2)	Photolytically stable	
Quantum yield of direct photo-transformation in water at Σ > 290 nm	No significant absorption > 290 nm. Therefore, quantum yield of direct photolysis has not been not determined.	
Flammability	Not highly flammable (flash point of 159 °C)	
Explosive properties	Not explosive	

Classification and proposed labelling

with regard to physical/chemical data	none
with regard to toxicological data	GHS07, Warning Irritating to eyes, category 2; H319: Causes serious eye irritation
with regard to fate and behaviour data	none
with regard to ecotoxicological data	none

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	Gas-chromatography with flame ionisation detection
Impurities in technical active substance (principle of method)	Gas-chromatography with flame ionisation detection

Analytical methods for residues

Soil (principle of method and LOQ)	Not required: significant residues of IR3535® in soil can be excluded.
Air (principle of method and LOQ)	Not required: IR3535® -based insect repellents spray applications involve large droplets which are not respirable.
Water (principle of method and LOQ)	Solid phase extraction (SPE) and UPLC-MS/MS detection (LOQ = 0.1 µg/L)
Body fluids and tissues (principle of method and LOQ)	Not required: IR3535® is not classified as toxic.
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not required: IR3535®-based insect repellent products are not used in a manner which may cause contact with such materials.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (	Not required: IR3535®-based insect repellent products are not used in a manner which may cause contact with such materials.

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	In rats about 90 % of the orally administered dose was excreted via urine (80 %) and faeces (10 %) within 72 hours. Following oral application to dogs peak plasma levels were reached after 1 hour. These results indicate fast and complete absorption from the GIT after oral administration.
Rate and extent of dermal absorption:	Dermal absorption was studied in the rat and the rabbit, using human tissue, and in human volunteers. Rat: Readily absorbed when applied as cream formulation (peak plasma levels after 30 min), slower when applied as pure active substance (peak plasma levels after 8 hours). Human: Readily absorbed when applied as water/ethanol based 20 % IR3535® model spray formulation (plasma levels peaked after 2-6 hours; urine levels peaked after 4-8 hours). The most absorption takes place in the first 6 hours after application with no further evidence of absorption beyond this time point. For the pure active substance and previously studied cream formulations our conclusions on dermal penetration are based on the *in vivo* animal studies and the human skin *in vitro* study. For a 24 hour application, a dermal penetration of 50 % was determined. For a more typical use pattern of 10 hours, a less reliable dermal penetration of 30 % was determined/extrapolated for the previously studied cream formulations. However, for water/ethanol-based 20 % IR3535® market formulations a dermal penetration of 14 % was determined for a 12 hour exposure (~ typical use condition of 10 hours) based on the outcome of the human volunteer study. Based on the findings of this study, a dermal absorption of 14 % is also valid for an exposure of 24 hours. The water/ethanol-based 20 % IR3535® market spray formulation used in this volunteer study represents a worst case formulation with regard to skin penetration (main component is ethanol, and in addition contains other well known enhancers of skin penetrating properties of substances). Therefore, a dermal absorption of 14 % derived from this study is also relevant for 20 % IR3535® lotion/cream formulations. **Dermal penetration of 14 %** based on *in vivo* human data.
Distribution:	Evenly over the whole body.
Potential for accumulation:	No
Rate and extent of excretion:	72 hours after oral administration in rats: 80 % of the administered dose was excreted via urine, 10 % via

	faeces, 0.5 % via exhaled air. Following oral application to dogs concentrations in plasma decreased rapidly with half-lifes of 0.8 – 1.1 hours. 72 hours after dermal application: 19, 36 and 33 % of the applied dose was found in urine of rats treated with IR3535® formulations with an a.i. content of 0.1, 1, and 10 %, respectively. In faeces, a maximum of 3 % of the applied dose was found. 42 to 64 % of the applied dose was found on skin or bandages.
Toxicologically significant metabolite	N-acetyl-3-N-n-butylaminopropionic acid, main metabolite, rapidly formed and degraded, hence covered by toxicity tests on IR3535®.

Acute toxicity (Annex IIA, VI.6.1)

Rat LD_{50} oral	> 5000 mg/kg bw
Rat LD_{50} dermal	> 10000 mg/kg bw
Rat LC_{50} inhalation	> 5.1 mg/L
Skin irritation	No
Eye irritation	IR3535® caused mild eye irritation in the rabbit which was reversible and does not imply classification according to Directive 67/548/EC. Due to the stricter cut-off values in the CLP-Regulation (EC) No 1272/2008, IR3535® should be classified as an eye irritant (Category 2).
Skin sensitisation (test method used and result)	Not sensitising (Buehler method with three induction applications, 1 challenge)

Repeated dose toxicity (Annex IIA, VI. 6.3, 6.4, and 6.5)

Species/ target / critical effect	Rat: No findings (oral and dermal) Dog: Increased incidence of gastrointestinal symptoms without evidence of any physiological alterations: no trigger to lower the NOAEL(oral) Rabbit: Decreased food consumption, decreased body weight/body weight gain (oral) Skin reactions: erythema, oedema (dermal) Conclusion: The rabbit is the most sensitive species
Lowest relevant oral NOAEL	Rabbit (28-day oral study) NOAEL: 500 mg/kg bw/d (decreased food consumption during the first half of the study in males, and decreased bw (gain) in both sexes at 1500 mg/kg bw/d) Rabbit (developmental study) NOAEL: 300 mg/kg bw/d (decreased food consumption and bw gain during the first 3 days of dosing at 600 mg/kg bw/d)
Lowest relevant dermal NOAEL	$NOAEL_{local}$: 33.3 mg/kg bw/d (28-d, dermal, rabbit) $NOAEL_{systemic}$: 333.3 mg/kg bw/d (28-d, dermal, rabbit: highest dose tested) $NOAEL_{systemic}$: 3000 mg/kgbw/d (90-d, dermal, rat: highest dose tested)
Lowest relevant inhalation NOAEL	No data available. Inhalation toxicity not required as exposure to vapour is very low and aerosol particles generated when spraying are not in the respirable range (see Document IIIA, Section 6, Point 6.3.3/01 for a detailed justification).

Genotoxicity	Not genotoxic.

Carcinogenicity

Species/type of tumour	No study available. Waiver provided based on overall negative genotoxicity tests, two subchronic studies with no adverse effects up to the limit dose and no structural alerts in the active substance.
lowest dose with tumours	n.a.

Reproductive toxicity

Species/ Reproduction target / critical effect	Rat / no effect on reproduction / maternal mortalities
Lowest relevant reproductive NOAEL	$NOAEL_{parental}$ = 300 mg/kg bw/day (mortality at 1000 mg/kg bw/d) $NOAEL_{offspring}$ = 1000 mg/kg bw/day (highest dose tested) $NOAEL_{reproduction}$ = 1000 mg/kg bw/day
Species/Developmental target / critical effect	Rabbit, Rat / no effect on development / maternal: decreased food consumption and bw gain during the first 3 days of dosing at 600 mg/kg bw/d, and reduced defecation (rabbit)
Lowest relevant developmental NOAEL	Rabbit: NOAEL maternal: 300 mg/kg bw/d (decreased food consumption and bw gain during the first 3 days of dosing at 600 mg/kg bw/d, and reduced defecation) NOAEL developmental: 600 mg/kg bw/d (highest dose tested)

Neurotoxicity

Species/ target/critical effect	No study available. No neurotoxic effects observed in any other study, no structural alerts for neurotoxicity.
Lowest relevant neurotoxicity NOAEL	n.a.

Other toxicological studies

Neurotoxicity	See above
Toxic effects on livestock and pets	Toxicity studies with IR3535® have been performed via the oral, dermal and inhalative route in different animal species. The results obtained in these studies can be used for bridging studies on livestock and pets as the effects do not differ significantly between species.
Studies related to the exposure of the a.s. to humans	No studies available
Food and feeding stuffs	Not applicable, IR3535® is not intended to be used in areas where food is produced, stored, transported or processed.
Other tests related to exposure of the a.s. to human	Further studies are not necessary for the purpose of a

considered to be necessary	comprehensive evaluation of the a.s.
Tests to assess toxic effects from metabolites of treated plants	IR3535® is not intended to be used in products for action against plants. Therefore, the submission of data on metabolites generated by treated plants is not required.
Mechanistic studies	No studies necessary to clarify effects reported in toxicity studies.
Further human health related studies	Not required

Medical data

Medical surveillance data on manufacturing plant personnel	No reports available on adverse effects on workers of manufacturing plants
Direct observations, e.g. clinical cases, poisoning incidents	Very rare local skin reactions.
Health records, both form industry and any other sources	No data available, neither from industry nor any other source.
Epidemiological studies on the general population	No data available.
Diagnosis of poisoning including specific signs of poisoning and clinical tests	IR3535® is not classified as toxic via the oral, dermal, and inhalation route. Acute toxicity studies in **animals** show only unspecific signs of intoxication with complete recovery. Repeated toxicity studies did not show specific signs of toxicity e.g. histological changes in organs. Adverse effects consisted of reduced body weight and body weight gain as well as reduced food consumption. There are no data available on **humans**.
Sensitization/allergenicity observations	No reports of sensitising potential available.
Specific treatment in case of an accident or poisoning: first aid measures and medical treatment	In case of poisoning, symptomatic treatment is warranted. A specific antidote is not known. For details please refer to Document IIIA, Section 6, 6.12.7.
Prognosis following poisoning	Acute toxicity studies showed unspecific signs of toxicity with complete recovery. Repeated toxicity studies did not show specific signs of intoxication e.g. histological changes in organs. Adverse effects consisted of reduced body weight and body weight gain as well as reduced food consumption. For details please refer to Document IIIA, Section A6.12.5

Summary	**Value**	**Study/critical effects**	**Safety factor /absorption (%)**
Acute AEL	5 mg/kg bw/d	1) Rabbit, oral, developmental toxicity study.	100 100 %

		Decreased food consumption and bw gain during first 3 days of dosing, reduced defecation at 600 mg/kg bw/d. NOAEL: 300 mg/kg bw/d. 2) Rabbit, oral, 28-days toxicity study. Decreased food consumption during the first half of the study in males, and decreased bw (gain) in both sexes at 1500 mg/kg bw/d. NOAEL: 500 mg/kg bw/d.	
Medium-term AEL	5 mg/kg bw/d	1) Rabbit, oral, developmental toxicity study. Decreased food consumption and bw gain during first 3 days of dosing, reduced defecation at 600 mg/kg bw/d. NOAEL: 300 mg/kg bw/d. 2) Rabbit, oral, 28-days toxicity study. Decreased food consumption during the first half of the study in males, and decreased bw (gain) in both sexes at 1500 mg/kg bw/d. NOAEL: 500 mg/kg bw/d.	100 100 %
Long-term AEL	5 mg/kg bw/d (not applicable here, maximum number of application is 28 days per year)	1) Rabbit, oral, developmental toxicity study. Decreased food consumption and bw gain during first 3 days of dosing, reduced defecation at 600 mg/kg bw/d. NOAEL: 300 mg/kg	100 100 %

		bw/d. 2) Rabbit, oral, 28-days toxicity study. Decreased food consumption during the first half of the study in males, and decreased bw (gain) in both sexes at 1500 mg/kg bw/d. NOAEL: 500 mg/kg bw/d.	
ADI (if residues in food or feed)	not applicable, no residues in food or feed occur	n.a.	n.a.
ARfD (acute reference dose)	not applicable, no residues in food or feed occur	n.a.	n.a.

Acceptable exposure scenarios (including method of calculation)

Industrial Production/Formulation of active substance	Industrial production and formulation. Described in detail in Document II-B and II-C. There is no concern for industrial workers in the production and formulation of the active substance
Professional users	Not relevant
Non-professional users	Described in detail in Document II-B and II-C. There is no concern for adults and children using the biocidal product (spray/lotion formulation containing 20 % IR3535®) as a Repellent Subtype PT19.01.
Secondary exposure as a result of use	Described in detail in Document II-B and II-C. There is no concern for secondary exposure for adults and children from the use of the IR3535®-based formulation containing 20 % IR3535®, as a Repellent Subtype PT19.01.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	IR3535® is not degradable at pH 4 and 7. **DT_{50} at pH 9:** 12 °C 866.13 h (calculated) 25 °C 177 h 30 °C 97.6 h 40 °C 34.5 h 50 °C 11.61 h
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	The concentration values of IR3535® stayed constant in the test system and in the dark control. The test results show that IR3535® is not subject to photolytical degradation.
Readily biodegradable (yes/no)	Not readily biodegradable according to the results of two "ready test".
STP simulation test	Elimination: > 99 % after 28 days.
Water/sediment study:	
DT_{50} IR3535® water:	6.79 – 8.41 d (20 °C) / 12.88 – 15.59 d (12 °C)
DT_{90} IR3535® water:	22.6 – 27.9 d (20 °C) / 42.86 – 52.91 d (12 °C)
DT_{50} IR3535® free acid water (lag phase):	86.1 – 110 d (20 °C) / 163.29 – 208.61 d (12 °C)
DT_{90} IR3535® free acid water (lag phase):	286 – 364 d (20 °C) / 542.39 – 690.32 d (12 °C)
DT_{50} IR3535® free acid water (phase 2 rapid):	4.47 – 5.68 d (20 °C) / 8.48 – 10.77 d (12 °C)
DT_{90} IR3535® free acid water (phase 2 rapid):	14.9 – 18.9 d (20 °C) / 28.26 – 35.84 d (12 °C)
Biodegradation in seawater	Not relevant

Anaerobic water/sediment study: DT_{50} total systems (nonsterile) DT_{90} total systems (nonsterile) DT_{50} total systems (sterile) DT_{90} total systems (sterile) DT_{50} total systems (nonsterile) DT_{90} total systems (nonsterile)	Not relevant
Non-extractable residues	Not determined, not relevant
Distribution in water / sediment systems (active substance)	Not determined, not relevant
Distribution in water / sediment systems (metabolites)	Not determined, not relevant

Route and rate of degradation in soil

Mineralization (aerobic)	Not determined, not relevant
Laboratory studies (range or median, with number of measurements, with regression coefficient)	No study conducted, not relevant
Field studies (state location, range or median with number of measurements)	No study conducted, not relevant
Anaerobic degradation	Not determined, not relevant
Soil photolysis	Not determined, not relevant
Non-extractable residues	Not determined, not relevant
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Not determined, not relevant
Soil accumulation and plateau concentration	Not determined, not relevant

Adsorption/desorption

K_a , K_d $K_a$oc , $K_d$oc	K_a = 9.516 L/kg K_d = 40.4 L/kg	K_{aOC} = 475.25 L/kg K_{dOC} = 1136 L/kg
pH dependence (yes / no)	not investigated	

Fate and behavior in air

Direct photolysis in air	Not studied – no data request
Quantum yield of direct photolysis	No significant absorption > 290 nm. Therefore, quantum yield of direct photolysis was not determined.
Photo-oxidative degradation in air	DT_{50} of 13.16 hours (for OH radical reaction, 24-hr day) derived by the Atkinson method of calculation
Volatilization	Not studied - IR3535® is only slightly volatile (vapour pressure = 0.15 ± 0.01 Pa at 20 °C).

Monitoring data, if available

Soil (indicate location and type of study)	No data available, not relevant
Surface water (indicate location and type of study)	No data available, not relevant
Ground water (indicate location and type of study)	No data available, not relevant
Air (indicate location and type of study)	No data available, not relevant

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group) for IR3535

Species	Time-scale	Endpoint	Toxicity
Fish			
Zebra fish (*Brachydanio rerio)*	96 h	LC_{50}	> 100 mg ai/L
Invertebrates			
Daphnia magna	48 h	EC_{50}	> 100 mg ai/L
Algae			
Desmodesmus subspicatus	72 h	E_bC_{50} E_rC_{50}	> 100 mg ai/L > 100 mg ai/L
Microorganisms			
Activated sludge	3 h	EC_{20} EC_{50} EC_{80}	> 1000 mg ai/L > 1000 mg ai/L > 1000 mg ai/L

Effects on earthworms or other soil non-target organisms

Acute toxicity to earthworm	No data available, not relevant
Reproductive toxicity to earthworm	No data available, not relevant

Effects on soil micro-organisms

Nitrogen mineralization	No data available, not relevant
Carbon mineralization	No data available, not relevant

Effects on plants

Toxicity to plants	No data available, not relevant

Effects on terrestrial vertebrates

Acute toxicity to mammals	No data available, not relevant
Acute toxicity to birds	No data available, not relevant
Dietary toxicity to birds	No data available, not relevant
Reproductive toxicity to birds	No data available, not relevant

Effects on honeybees

Acute oral toxicity	No data available, not relevant
Acute contact toxicity	No data available, not relevant

Effects on other beneficial arthropods

Acute oral toxicity	No data available, not relevant
Acute contact toxicity	No data available, not relevant
Acute toxicity to ……	

Bioconcentration

Bioconcentration factor (BCF)	fish: 5.6 L/kg (calculated) earthworm: 1.44 kg/kg (calculated)
Depuration time(DT_{50}) (DT_{90})	No data available, not relevant
Level of metabolites (%) in organisms accounting for > 10 % of residues	No data available, not relevant

Chapter 6: Other End Points

Not applicable, no other end points

APPENDIX 2: LIST OF INTENDED USES[1]

Object and/or situation	Member State or Country	Product name	Organisms Controlled[*]	Formulation		Application			Applied amount per treatment	Remarks:
				Type	Conc. of as	method kind	number min max	interval between applications (min)	Amount of product applied to exposed parts of the body	
Biting and sucking insects	EU	n.a.; model formulation	***Mosquitoes*** *Anopheles spec* *Aedes spec* *Culex spec* *Mansonia spec* ***Ticks*** *Ixodes spec* ***Lice*** *Pediculus spec* ***Flies*** *Stomoxys spec* *Simuliidae* *Tabanidae* *Musca spec* *Phlebotomus spec* ***Wasps*** *Pollistes spec* ***Bees*** *Apis spec*	Lotion/ Spray	20% (w/w)	Direct application to skin by consumers.	Typically 1-2 times a day in the summer. Multiple applications are possible, when required.	When efficacy is noticeably reduced.	3 g of product is sufficient to cover approximately 50% of the total body surface of an adult.	The model formulation assessed in the dossier is only one example of commercially available repellents. Other formulation types that can be used are gels, aerosol sprays, wipes etc.. Products used for other applications than to human skin (i.e. application to human hair, textiles and insect nets, surfaces in households, or to animal skin/fur) may also be relevant for product authorisation.[**]

[1] adapted from: EU (1998a): European Commission: Guidelines and criteria for the preparation of complete dossiers and of summary dossiers for the inclusion of active substances in Annex I of Directive 91/414/EC (Article 5.3 and 8,2). Document 1663/VI/94 Rev 8, 22 April 1998

(*) If the applicant wants claims against other organisms, new data should be submitted at product authorisation level.
(**) New information should also be supplied to support specific label claims (on animal or other) at product authorisation stage.

APPENDIX 3: LIST OF STUDIES

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. For studies marked Yes(i) data protection is claimed under Article 12.1(c) (i), for studies marked Yes(ii) data protection is claimed under Article 12.1(c) (ii). These claims are based on information from the applicant. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
Anonymous	A3.4.1/02	not indicated	Proof of structure - Insekt-Repellent 3535; [redacted]; Study No.: 1/11887; (unpublished) Doc. No. 117-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Anonymous	A3.5/01	2005	Particle Size Distribution of WP-17-03 containing IR3535 when applied as a pump spray; Aeropump; Study No.: Not indicated; (unpublished) Doc. No. 214-001	Y (Data on existing a.s. submitted for the 1st time for entry in Annex I.)	MERCK KGaA
Anonymous	A5.3.1/02	1989-1990	Field Test of IR-3535 (Insect repellent); [redacted] Study No.: Not indicated; (unpublished) Doc. No. 336-1902	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.2/05	1996	Insect repellent 3535 (Art. No. 111887) - 28-day toxicokinetic study with dermal application to rats; [redacted]; Study No.: 398823; GLP; (unpublished) Doc. No. 532-005	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Axt, A. Arras, J	B7.5/01	2006	Determination of IR3535® amount after spray application; Study No.: LA 06 010, (unpublished). Doc. No. 783-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.2)	1980	Expert report on the tolerance of insect repellents when applied to mucous membranes (Translation from German); [redacted]; Study No.: 15.doc; (unpublished) Doc. No. 566-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.2)	1981	Acute toxicity of insect repellent No. 127 (Translation from Germany); [redacted]; Study No.: E01.doc; Not GLP; (unpublished) Doc. No. 581-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
Benzon, G.L;	A5.3.1/09	1996	Results of *in vitro* assay of Merck KGaA Insect Repellent 3535 against nymhal deer ticks, *Ixodes scapularis*; [redacted]; Study No.: IR 3535-PA-95.03; (unpublished) Doc. No. 336-1909	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.1.4/04	1996	Test for skin irritation in humans, modified Duhring chamber test; [redacted]; (unpublished) Doc. No. 565-004	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Bremmer, H.J. Prud'homme de Lodder, L.C.H. Van Engelen, J.G.M	Doc IIB (8.2)	2006	RIVM report 320104001/2006 Cosmetic Fact Sheet To assess the risks for the consumer	N	
[redacted]	A5.3.1/08	not indicated	Repellent action of Insect Repellent 3535 against Ixodes ricinus ticks (Acari: Ixodidae); [redacted]; (unpublished) Doc. No. 336-1908	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A5.3.1/06	1995	Report of tests of repellency of evaporated formulations of the insect repellent IR 3535 on houseflies, *Musca domestica*; [redacted]; Study No.: MER/FLM/REP (unpublished) Doc. No. 336-1906	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.2/03	1996a	Insect repellent 3535 (Art. No. 111887) dermal absorption and pharmacokinetic study on various organs and tissues of male rats and excretion pattern of radioactivity after single dermal administration of the 14C-labelled compound [redacted]; Study No.: 398147; GLP; (unpublished) Doc. No. 511-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.2/04	1996b	14C-Insect repellent 3535 (Art. No. 111887): Bioretention study in male rats after single dermal administration of the 14C-labelled compound at a dose level of 1.0 mg/cm²; [redacted]; Study No.: 612966; GLP; (unpublished) Doc. No. 511-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Buttler, O.	A4.2c/01	2012	Art. 111887 (IR3535®) and IR3535-free acid, Residue Analytical Method for the Determination in Surface Water	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	Doc III B 5.10/11	2007	Test of Personal Insect Repellents - Volume 10 [redacted] Report No.: EMD-003.3 (Aerosol) EMD-003 GLP, unpublished Doc. No.: 336-1914	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	Doc III B 5.10/12	2007	Test of Personal Insect Repellents - Volume 11 [redacted] Report No.: EMD-004.3 (Aerosol) EMD-004 GLP, unpublished Doc. No.: 336-1915	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	Doc III B 5.10/13	2006	Test of Personal Insect Repellents: Study EMD-003.1 - Replacement for MRID 46979001 - Volume 11 [redacted] Report No.: EMD-003.1 (Lotion) EMD-003 GLP, unpublished Doc. No.: 336-1916	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	Doc III B 5.10/14	2006	Test of Personal Insect Repellents: Study EMD 004.1 - Replacement for MRID 4699003 - Volume 12 [redacted] Report No.: EMD-004.1 (Lotion) EMD-004 GLP, unpublished Doc. No.: 336-1917	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	Doc III B 5.10/15	2006	Test of Personal Insect Repellents: Study EMD 003.2 - Replacement for MRID 46979002 - Volume 11 [redacted] Report No.: EMD-003.2 (Pump Spray) EMD-003 GLP, unpublished Doc. No.: 336-1918	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	Doc III B 5.10/16	2006	Test of Personal Insect Repellents: EMD 004.2 - Replacement for MRID 46979004 - Volume 12 [redacted] Report No.: EMD-004.2 (Pump Spray) EMD-004 GLP, unpublished Doc. No.: 336-1919	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	A5.3.1/10	1996	Laboratoy evaluation for the efficacy of Merck KGaA, Insect Repellent 3535 against stable flies and deer ticks; [redacted]; Study No.: IR 3535-FL-95.01; (unpublished) Doc. No. 336-1911	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
Cilek, J.E. Petersen, J.L. Hallmon, C.F.	A5.3.1/15	2004	Comparative efficacy of IR3535 and DEET as repellents against adult *Aedes aegypti* and *Culex quinquefasciatus*; Journal of Amercan Musquito Control Association, 20(3): 299-304; (published) Doc. No. 392-003	N	
[redacted]	A5.3.1/05	1993	Bioclinical *in vivo* trial to test the efficacy of repellent lotions (insect repellent 3535) in order to prevent re-infestation of lice on humans after the us of a pediculicidal shampoo; [redacted]; Study No.: AC 93-02; (unpublished) Doc. No. 336-1905	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A5.3.1/03	1992	Evaluation of repellents on mouses; [redacted]; (unpublished) Doc. No. 336-1903	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Costantini, C. Badolo, A. Ilboudo-Sanogo, E.	A5.3.1/14	2003	Field evaluation of the efficacy and persistence of insect repellents DEET, IR3535, and KBR 3023 against *Anopheles gambiae* complex and other Afrotropical vector mosquitoes; Transactions of the Royal Society of Tropical Medicine and Hygiene 98: 644-652; (published) Doc. No. 392-002	N	
[redacted]	Doc IIA (3.6)	1982	An investigation into the possible induction of mutations at the HGPRT-Locus of chinese hamster ovary cells by "insekt-repellent 3535"; [redacted]; Study No.: CL 82/144; GLP; (unpublished) Doc. No. 557-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
ECB	Doc II	2003	Technical Guidance Document (TGD) on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.	N	
ECB	Doc II	2000	Technical Guidance Document in support of the Directive 98/8/EC concerning the placing of biocidal products on the market. Guidance on Data Requirements for Active Substances and Biocidal Products	N	

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
ECB	Doc. II	2002	Technical Notes for Guidance on Dossier Preparation including preparation and evaluation of study summaries under Directive 98/8/EC Concerning the Placing of Biocidal Products on the Market Part I Dossier Preparation	N	
ECB	Doc. II	2002	TNsG on Annex I inclusion - Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council Concerning the Placing of Biocidal Products on the Market. Principles and Practical Procedures for the inclusion of active substances in Annexes I, IA and IB	N	
ECB	Doc IIB	2002	Technical Notes for Guidance (TNsG) Human exposure to biocidal products (2002)	N	
EUBEES	Doc. IIB	2004	Suplement to the methodology for risk evaluation of biocides. Environmental Emission Scenarios for biocides used as hyuman hygiene biocidal products (Product type I)	N	
[redacted]	A6.2/01	1996	Synthesis and in vivo-stability of a 14C-labelled material; [redacted]; Study No.: 16/16/96; (unpublished) Doc. No. 414-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.13/01	2005	Determination of surface tension (OECD ring method); [redacted]; Study No.: 111887; GLP; (unpublished) Doc. No. 116-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.1.1.2.1/02	2011	Art. 111887 (IR3535®) - Ready biodegradability modified Sturm test [redacted] Report No.: 101209MB AST14171 GLP, unpublished Doc. No.: 713-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.1.2.2.2/01	2012	Insect Repellent ^{14}C-IR3535®, Aerobic transformation in aquatic sediment systems using ^{14}C-labelled test item	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	B3.5/01	2008	Determination of the acidity or alkalinity and the pH value of WP-17-09; Source: [redacted]; Report No.: 43801349; GLP; (unpublished) Doc. No.: 215-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	B3.4/01	2008	WP-17-09 and WP-17-10 - Test according to the official journal of the european community (Explosive and oxidizing properties of solids and liquids); Source: [redacted]; Report No.: WL/CAS/BC6; (unpublished) Doc. No.: 242-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Gal-Bogunà Vinals, E. Comellas Riera, L.	A2.8/01	1997	Caracteristicas de la muestra IQS - Institut Químic de Sarriá, Barcelona, Spain Report No.: 161-T97/4300355 64-E97 Not GLP, unpublished Doc. No.: 131-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	A6.1.3/01	1996	Study on the acute inhalation toxicity LC50 of Art. Nr. 111887 (Insekt-Repellent 3535) as a liquid aerosol in rats 4-hour exposure (Revised July 8, 1996); BASF AG, Ludwigshafen, Germany; Study No.: 13I0189/957012 957012EPA; GLP; (unpublished) Doc. No. 523-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.8.1/02	1996	Insect repellent 3535 (Article Number 111887) - Developmental toxicity study with oral administration to rabbits; [redacted]; Study No.: T 9382; GLP; (unpublished) Doc. No. 551-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.8.2/01	1997	Insect repellent 3535 (Article Number 111887) - 2-Generation study with oral administration to rats - 3 Volumes; [redacted]; Study No.: T 9381; GLP; (unpublished) Doc. No. 553-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.2/07	1997	Insect repellent 3535 (Article Number 111887) - Investigatory study T 9400 with oral administration to Himalayan and New Zealand White Rabbits; [redacted]; Study No.: T9400I-Ü.DOC; (unpublished) Doc. No. 531-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.8.1/03	1997	Insect repellent 3535 (Article Number 111887) - Investigatory study T 9385 with oral administration to rabbits; [redacted]; Study No.: 1257T93851NV.DOC; GLP; (unpublished) Doc. No. 531-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.3.1/01	2005	Estimation of photochemical degradation of IR3535 using the Atkinson method; [redacted]; Study No.: 743-001; (unpublished) Doc. No. 743-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	A3.8/01	2006	Statement regarding the stability of IR3535® in organic solvents Study No.: 819-004 Doc. No. 114-06	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.6.3/01	1996	Insect repellent 3535 (Art. No. 111887) - Mammalian cell (V79) gene mutation test; [redacted]; Study No.: AFP 128; GLP; (unpublished) Doc. No. 557-007	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.4.1.4/01	2001	Toxicity of Art. 111887 (IR 3535) to activated sludge in a respiration inhibition test; [redacted]; Study No.: 9581171; GLP; (unpublished); Doc. No. 842-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.1.1/01	1997	Insect repellent 3535 (Article Number 111887) - Acute toxicity study in rats after oral administration; [redacted]; Study No.: T14215; GLP; (unpublished) Doc. No. 521-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.1.4/01	1996	Insect repellent 3535 (Article Number 111887) - Primary eye irritation test in rabbits; [redacted]; Study No.: T13919 40/12/96; GLP; (unpublished) Doc. No. 566-004	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.4.1.1/01	2000	Aquatic Toxicoloy - Art. 111887 (IR3535) - Acute toxicity study in Zebra fish (Brachydanio rerio); [redacted]; Study No.: T14775; GLP; (unpublished) Doc. No. 821-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.4.1.2/01	2000	Aquatic Toxicology - Art. 111887 (IR3535) - Acute immobilization test in Daphnia magna; [redacted]; Study No.: T14774; GLP; (unpublished) Doc. No. 822-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.4.1.3/01	2001	Aquatic Toxicology - Art. 111887 (IR 3535) - Algae growth inhibition test in Desmodesmus subspicatus; [redacted]; Study No.: T14776; GLP; (unpublished) Doc. No. 823-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.3)	1972	Tolerance test of repellents BE 3304 and BE 3535 on mucous membranes - (Translation from German); Not indicated; Study No.: E14.doc; (unpublished) Doc. No. 566-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	Doc IIA (3.3)	1972	Tolerance test of repellents BE 3535 (purified) on mucous membranes of rabbits eyes - as agreed upon by telephone - (Translation from German); Not indicated; Study No.: E16.doc; (unpublished) Doc. No. 566-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	B3.7/01	2008	Storage stability of IR3535 based biocidal products; Source: [redacted]; (unpublished) Doc. No.: 245-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A5.3.1/11	1995	In vitro assay to determine the efficacy of Merck KGaA, Insect Repellent 3535 against black flies, deer flies and stable flies; [redacted]; Study No.: IR 3535-CN-95.02; (unpublished)	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.6)	1980	Trial in vitro for mutagenic potential in bacteria with and without addition of a metabolizing system; [redacted]; Study No.: 4/141/80; (unpublished) Doc. No. 557-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Kröpke, R. Benner, G. Schulz, J. Wittern, K.P. Hill, A. Beyer, N.	A5.3.1/18	2007	Field Evaluation of the Efficacy of proprietary Repellent Formulations with IR3535® and Picaridin against medically important mosquitos in the Bolivian Amazon Region; IMED (International Meeting on emerging diseases and surveillance), Vienna, 2007; (published) Doc. No. 392-007	N	
[redacted]	A7.1.1.2.1/01	2000	Ready biodegradability of Art. 111887 (IR 3535) in a closed bottle test; [redacted]; Study No.: USF-AL-04-00; GLP; (unpublished) Doc. No. 713-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.2/06	1996	Insect repellent 3535 (Art. No. 111887) in vitro metabolism in hepatocytes of rat and man; [redacted]; Study No.: 16/34/95; Not GLP; (unpublished); Doc. No. 514-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A5.3.1/04	1993	Report on the laboratory trial of insect repellent 3535 and of a reference repellent DEET against *Pediculus humanus*; [redacted]; Study No.: AC 93-01; (unpublished) Doc. No. 336-1904	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
Leal, W.S.	A5.4.1/01	2005	Molecular-based chemical prospecting of mosquito attractants and repellents; Source: Insect Repellents, CRC Press, Taylor & Francis Group, 2007, ISBN 0-8493-7196-1: Insect Repellents, Principles, Methods, and Uses, 2005, 11, 229-242; (published) Doc. No.: 392-004	No	
[redacted]	Doc IIA (3.2)	1973	Acute toxicity of BE 3535 after oral administration to rats (Translation from German); [redacted]; Study No.: E02.doc; (unpublished) Doc. No. 521-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.2)	1981	Acute oral toxicity of BE 3535 after administration to mongrel dogs (pilot study) (Translation from German); [redacted]; Study No.: E03.doc; (unpublished) Doc. No. 521-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.1.2/01	1973	Acute toxicity of BE 3535 after local application to 1/10 of the body surface of rats; [redacted]; Study No.: E07.doc; (unpublished) Doc. No. 522-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.2)	1981	Acute toxicity of BE 3535 after local application to 1/10 of the body surface of mice (pilot study) - (Translation from German); [redacted]; Study No.: E05.doc; unpublished) Doc. No. 522-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.2)	1981	Acute toxicity of BE 3535 after local application to 1/10 of the body surface of beagle dogs (pilot sutdy); [redacted]; Study No.: E06.doc; (unpublished); Doc. No. 522-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.1.4/02	1973	Local tolerance test of different preparations of BE 3767 and of BE 3535 in rabbits (Patch test) - (Translation from German); [redacted]; Study No.: E12.doc;; (unpublished) Doc. No. 565-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.2)	1981	4 week toxicity of the repellent BE 3535 in beagle dogs after administration by gavage; [redacted]; Study No.: E09.doc; (unpublished) Doc. No. 532-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	A6.3.1/01	1974a	4 week toxicity of BE 3535 in sprague-dawley rats after administration in the diet; [redacted]; Study No.: E08.doc; (unpublished) Doc. No. 532-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.3.1/02	1974b	4 week toxicity of the repellent BE 3535 in New Zealand White rabbits after administration by gavage; [redacted]; Study No.: E08.doc; (unpublished) Doc. No. 532-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.3.2/01	1974c	Local and general (systemic) tolerance test of BE 3535 with 4 week application to the dorsal skin of NZW rabbits; [redacted]; Study No.: E13.doc; (unpublished) Doc. No. 532-004	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.8.1/04	1975b	The effect of BE 3535 on the pregnant rat and the fetus after administration by gavage (pilot study with 1 dose level) - (Translation from German); [redacted]; Study No.: E23.doc; (unpublished) Doc. No. 551-002	Y (Data on existing a.s, submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.8)	1975a	The effect of BE 3535 on the pregnant New Zealand White Rabbit and the fetus after administration by gavage (pilot study with 1 dose level); [redacted]; Study No.: E22.doc; (unpublished) Doc. No. 551-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A5.3.1/01	1981	Efficiency data of insect repellent 3535; [redacted]; Study No.: SJ02 0001.0.0; (unpublished) Doc. No. 336-1901	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A2.7/01	2013	IR 3535® (insect repellent 3535): production results Merck, S.L., Mollet del Vallès, Spain Report No.: na Not GLP, unpublished Doc. No.: 172-002	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	A2.8/02	2013	Insect Repellent IR3535® Impurity Profile Report Merck, S.L., Mollet del Vallès, Spain Report No.: na Not GLP, unpublished Doc. No.: 172-003	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
[redacted]	A4.1/02	2012	Analytical Method Report for the Determination of Insect Repellent IR3535® Merck, S.L., Mollet del Vallès, Spain Report No.: ni Not GLP, unpublished Doc. No.: 412-001	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	A6.6.4/01	1996	Insect repellent IR 3535 (Art. No. 111887)- Induction of micronuclei in the bone marrow of treated mice; [redacted]; Study No.: 221/12-1052; GLP; (unpublished); Doc. No. 557-004	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.6.4/02	1999a	Insect repellent IR 3535 (Art. No. 111887)- Collection of plasma and bone marrow samples from treated mice; [redacted]; Study No.: 70/71-D5140; GLP; (unpublished) Doc. No. 512-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.6.4/03	1999b	Insect repellent IR 3535 (Art. No. 111887)- Induction of chromosome aberrations in the bone marrow of treated rats; [redacted]; Study No.: 70/76-D5140; GLP; (unpublished) Doc. No. 557-006	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.5/02	2002	Determination of the solubility of Art. 111887 (IR 3535) in three different buffer solutions; [redacted]; Study No.: 12863185; GLP; (unpublished) Doc. No. 114-005	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.1.1.1.1/01	2002	Test for determination of the hydrolysis of Art. Nr. 111887 (IR 3535); [redacted]; Study No.: 12861193; GLP; (unpublished) Doc. No. 711-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.1.3/01	2002	Determination of the adsorption / desorption behaviour of Art. Nr. 111887 (IR 3535); [redacted]; Study No.: 12862195; GLP; (unpublished) Doc. No. 731-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc III B 5.10/17	2009	Bioclinical trial to study the efficacy of a product containing - Repellent 3535 [redacted] Report No.: 09-01 Not GLP, unpublished Doc. No.: 336-1920	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	MERCK KGaA
Milutinovic, R. Milic J. Stajkoviv N. & Cvetkovic A.	A5.3.1/13	2000	Influence of o/w emulsion composition with polymeric emulsifier on repellents efficiency; 19th Phamaceutical Technology Conference, Volume 2: 365-372; (published) Doc. No. 392-001	N	N.A.
[redacted]	A6.1.5/01	1997	Delayed contact hypersensitivity study in guinea pigs; [redacted]; Study No.: 96-8304-21; GLP; (unpublished) Doc. No. 567-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	A6.6.2/02	1996	Mutagenicity test on IR 3535. Chromosomal aberrations in chinese hamster ovary (cho) cells with and without exogenous metabolic activation; [redacted]; Study No.: 17982-0-437; GLP; (unpublished) Doc. No. 557-005	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Naucke, T.J. Lorentz, S Grünewald, H.-W.	A.5.3.1/16	2006	Laboratory testing of insect repellents IR3535® and DEET against *Phlebotomus mascittii* and *P. dubosqi* (Diptera: Psychodidae), International Journal of Medical Microbiology 296 (SI), 230-222 (published) Doc. No. 392-005	N	
Naucke, T.J. Kröpke, R. Benner, G. Schulz, J. Wittern, K. P. Rose, A. Krückel, U.	A5.3.1/17	2007	Field evaluation of the efficacy of proprietary repellent formulations with IR3535® and Picaridin against *Aedes eagypti*; Parasitology Research; founded as Zeitschrift für Parasitenkunde, Springer Verlag, 2007; (published) Doc; No. 392-006	N	
[redacted]	A3.15/01	2005	IR3535 - Explosive Properties, Oxidising Properties; [redacted]; Study No.: Not indicated; (unpublished) Doc. No. 141-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.4.2/01	1996	Insect repellent 3535 (Art. No. 111887) - 90-day subchronic toxicity study with dermal application to rats (2 Volumes); [redacted]; Study No.: 398834; GLP; (unpublished) Doc. No. 534-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.1.2.1.1/01	2006	Degradation of Art. 111887 (IR3535®) in an Aerobic Sewage Treatment Simulation Test in the Laboratory; [redacted]; Study No.: 28521170; GLP; (unpublished) Doc. No. 713-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A5.3.1/07	1995	Study on the repelling potential of a cosmetic composition on wasps and honeybees; [redacted]; Study No.: BT 7695; (unpublished) Doc. No. 336-1907	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.1.4/05	1986	Investigation for phototoxic potential with Insekt-Repellent 3535 Art.-Nr. 11887 in albino guinea pigs; [redacted]; Study No.: 061773; GLP; (unpublished) Doc. No. 565-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.1.5/02	1986	Determination of photoallergenic potential with Insekt-Repellent 3535, Art.- Nr. 11887 in albino guinea pigs; [redacted]; Study No.: 061762; GLP; (unpublished) Doc. No. 567-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	Doc IIA (3.5)	1997	A two-week repeated dose toxicity study of IR 3535 in non-pregnant rabbits; [redacted]; Study No.: WILL-149022; GLP; (unpublished) Doc. No. 531-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	Doc IIA (3.8)	1997a	A dose range-finding developmental toxicity study of IR 3535 in rabbits; [redacted]; Study No.: WIL-149020; GLP; (unpublished) Doc. No. 551-005	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.8.1/01	1997b	A developmental toxicity study of IR 3535 in rabbits; [redacted]; Study No.: WIL-149021; GLP; (unpublished) Doc. No. 551-004	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A6.4.1/01	2006	ART. 111887 (IR3535) - 3 month oral toxicity study in beagle dogs with a 6 week recovery period[redacted]; Study No.: 090006d18056b262v1.0; GLP; (unpublished) Doc. No. 533-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	B3.6/01	2008	Determination of the relative density of liquids - WP-17-09; Source: [redacted]; Report No.: 01/08; GLP; (unpublished) Doc. No.: 213-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	B3.2/01	2008	WP-17-09 (Batch No. ML-180308) - Flash point A.9. - Auto-flammability (Determination of the temperature of self-ignition of volatile liquids and of gases) A.15.; Source: [redacted]; Report No.: 20080422.01; GLP; (unpublished) Doc. No.: 241-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Thavara, U. Tawatsin, A. Chompoorsri, J. Suwonkerd, W.	A5.3.1/12	2001	Laboratory and field evaluations of the Insect repellent 3535 (Ethyl Butylacetylaminopropionate) and DEET against mosquito vectors in Thailand;Journal of the American Musquito Control Association, 17(3):190-195; (published) Doc. No. 336-1913	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	
[redacted]	A6.6.1/01	1996	Insect repellent 3535 (Art. No. 111887) - Bacterial mutagenicity assay, Salmonella typhimurium and Escherichia coli; [redacted]; Study No.: T13942 40/53/96; GLP; (unpublished) Doc. No. 557-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted] [redacted]	A6.6.2/01	1999	Genotoxicity - Art. 111887 (Insect Repellent IR 3535) - In vitro chromosome aberration assay in V79 chinese hamster cells; [redacted]; Study No.: T14376; GLP; (unpublished) Doc. No. 557-008	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	A6.2/08	2002	In vitro percutaneous absorption study with IR3535 through viable human skin membranes; [redacted]; Study No.: V99.1029 010.40904; GLP; (unpublished) Doc. No. 511-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.5/01	1997	Determination of the water solubility of insect-repellent 3535 (TGAI) - including development and validation of a high performance liquid chromatography method; [redacted]; Study No.: 183645; GLP; (unpublished) Doc. No. 114-004	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.9/01	1996	Determination of the partition coefficient (N-Octanol/Water) of insect-repellent 3535 (TGAI); [redacted]; Study No.: 183656; GLP; (unpublished) Doc. No. 114-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.17/01	1996	Determination of the stability of insect-repellent 3535 (TGAI) to metals and metal ions; NOTOX B.V., 's-Hertogenbosch, Netherland; Study No.: 183768; GLP; (unpublished) Doc. No. 146-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
van der Poel, P.	Doc. IIB	2001	RIVM report 601450008 Supplement to the methodology for risk evaluation of biocides. Emission Scenraio document for Product Type 2: Private and public health area disinfectants and other biocidal products (sanitary and medical sector).	N	
[redacted]	A6.2/02	1996	Insect repellent 3535 (Art. No. 111887)-Pharmacokinetics and metabolism study after intravenous and dermal application of the 14C-labelled compound to male rats and rabbits; [redacted]; Study No.: 392883; GLP; (unpublished) Doc. No. 512-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
Van Engelen, J.G.M Prud'homme de Lodder, L.C.H	Doc IIB (8.2)	2007	RIVM report 320104001/2007 Non-food products: how to assess children's exposure?	N	
[redacted]	A3.17/02	1998	Determination of the storage stability and corrosion characteristics of insect-repellent 3535 (TGAI) over 1 year; [redacted]; Study No.: 183678; GLP; (unpublished) Doc. No. 146-003	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	A3.1.2/01	1997	Determination of the boiling temperature of insect-repellent 3535 (TGAI); [redacted]; Study No.: 183612; GLP; (unpublished) Doc. No. 112-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.1.3/01	1996	Determination of the density (Liquid) of insect-repellent 3535 (TGAI); [redacted]; Study No.: 183623; GLP; (unpublished) Doc. No. 113-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.2/01	1997	Determination of the vapour pressure of insect-repellent 3535 (TGAI); [redacted]; Study No.: 183634; GLP; (unpublished) Doc. No. 115-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.3.1/01	1996	Determination of appearance of insect-repellent 3535 (TGAI); [redacted]; Study No.: 183601; GLP; (unpublished) Doc. No. 111-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.4.1/01	1996	Determination of the UV-VIS absorption spectra of insect-repellent 3535 (TGAI); [redacted]; Study No.: 193332; GLP; (unpublished) Doc. No. 117-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.10/01	1996	Determination of the accelerated storage stability of insect-repellent 3535 (TGAI) by heating; [redacted]; Study No.: 183757; GLP; (unpublished) Doc. No. 141-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.12/01	1996	Determination of the flash-point of insect-repellent 3535 (TGAI); [redacted]; Study No.: 183667; GLP; (unpublished) Doc. No. 142-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.14/01	1997	Determination of the viscosity of insect-repellent 3535 (TGAI); [redacted]; Study No.: 183713; GLP; (unpublished) Doc. No. 116-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A3.7/01	1996	Determination of the solubility of insect-repellent 3535 (TGAI) in 6 organic solvents; [redacted]; Study No.: 183735; GLP; (unpublished) Doc. No. 114-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA
[redacted]	A7.1.1.1.2/01	1997	Direct Phototransformation of Insect-Repellent 3535 (TGAI) in water; [redacted]; Study No.: 184433; GLP; (unpublished) Doc. No. 712-001	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA

Author(s)	Section No. / Reference No.	Year	Title, Source (laboratory), Report No., GLP, (Un)Published	Data Protection (Yes/No)	Owner
[redacted]	A6.1.4/03	1977	Topical hazard evaluation program of candidate insect repellent A13-70763 3[N-n-BUTYL-N-ACETYL] aminopropionic acid-ethyl ester; [redacted]; Study No.: 51-0014-77 (unpublished) Doc. No. 581-002	Y (Data on existing a.s. submitted for the first time for entry in Annex I.)	MERCK KGaA