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# Interceptor® G2 –

## first-in-class dual active ingredient insecticide treated net (ITN) to control insecticide-resistant mosquitoes and reduce malaria transmission

# Content

# Interceptor® G2 – Innovative second-generation insecticide treated net (ITN)

- First in class dual active ingredient. ITN providing Public Health Value
- Only dual active ingredient ITN with proven efficacy reducing malaria transmission
- Innovative active ingredient system formulated with alpha-cypermethrin and chlorfenapyr
- New mode of action provided by chlorfenapyr
- Highly effective against insecticide-resistant mosquitoes
- Based on well proven BASF technology used in Interceptor® ITN
- Ready and safe to use
- Proven long lasting efficacy after 20 washes
- WHO PQ listed

## Introduction and background

The best method to lessen the burden of malaria is through prevention. Bed nets, one of the current tools approved by the World Health Organization (WHO), have been used for centuries as physical barriers against mosquitoes – even dating back to ancient Egypt. Beginning in the 1980s, bed nets were treated with insecticides to control mosquitoes. The dipping of nets in insecticide treated water baths provided further personal protection, thus disrupting the transmission of malaria. However, nets required retreatment every six months which posed a challenge to maintain at the household level. Beginning in the 21st century, this process was improved by the development of insecticide-treated nets (ITN) making them wash resistant and more evenly treated. The new ITN technology provided longer efficacy, enabled easier handling and proved safer to the user as no chemical retreatment is required.

In comparison to other Public Health interventions for malaria prevention, such as Indoor Residual Spray (IRS), ITNs also empower the individual to participate personally in their protection against malaria as ITN are tangible and visible. This has made ITN a huge success in the malaria prevention as an astonishing 2.9 bn ITNs have been distributed globally from 2004 to 2022. It is estimated that the distribution of the ITNs in sub-Saharan Africa, where the majority of cases occurs, averted 457 million cases (uncertainty interval: 418–484 million cases)[2]. In 2021, global malaria cases were estimated at 247 million[3].

The golden standard and the only insecticide class used so far to treat bed nets are pyrethroids. The pyrethroids are excellent for the use on ITNs based on the following properties:

- Low toxicity to humans, safe to use
- Cheap active ingredient (a.i.) and readily available
- Excellent efficacy against mosquitoes in general (neurotoxic with fast killing results; effective knock-down providing personal protection; acts as a repellent)

In addition, the chemical-physical profile of pyrethroids is perfect for the application on ITN:

- Solid at room temperature
- Very low solubility in water – the active ingredient survives 20 washes
- Very low vapor pressure minimizing losses during production and use
- Easy to handle in production of ITN for both coated PET and incorporated PE
- Standard textile production processes suitable without losing active ingredient

# Insecticide resistance

This success story of pyrethroids based ITNs is one of the reasons for the development of insecticide resistance in mosquitoes on a global level and more intensely in malaria endemic regions of Sub-Saharan Africa (Figure 2). Resistance to pyrethroid is ubiquitous throughout all subregions of Africa[4]. At the same time, the application of other insecticide classes such as organochlorines, organophosphates, and carbamates in other Public Health interventions – like IRS – increases the chances of insecticide resistance (Figure 1).

Leading experts consider this situation a threat to malaria control, especially with the limited toolbox of available Public Health insecticide classes. The Public Health community is urgently requesting the development and introduction of new active ingredients with different mode of actions (MoA)[5]. This is especially true in the case of ITNs, where the dependence on one insecticide class is the biggest risk.

The Global Plan for Insecticide Resistance Management (GPIRM[6]) recommends the use of insecticide mixtures as one of several strategies for successful Insecticide Resistance Management (IRM). This strategy can have a dramatic effect on populations of resistant vectors by exposing them to multiple insecticides. ITN products containing a mixture of novel active ingredients could be effective in delaying the evolution of insecticide resistance.

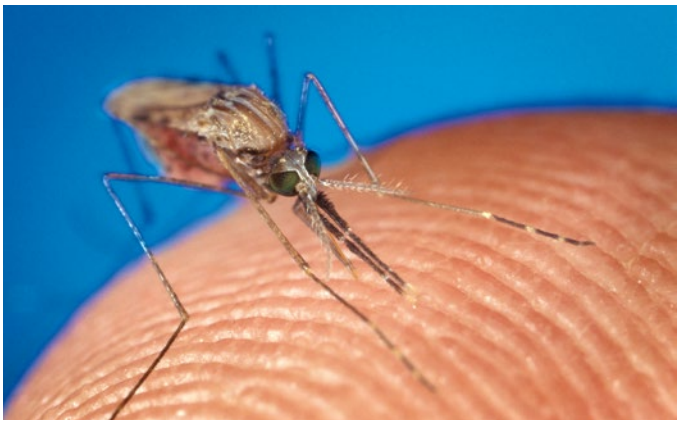


**Figure 1:** Development and status of insecticide resistance

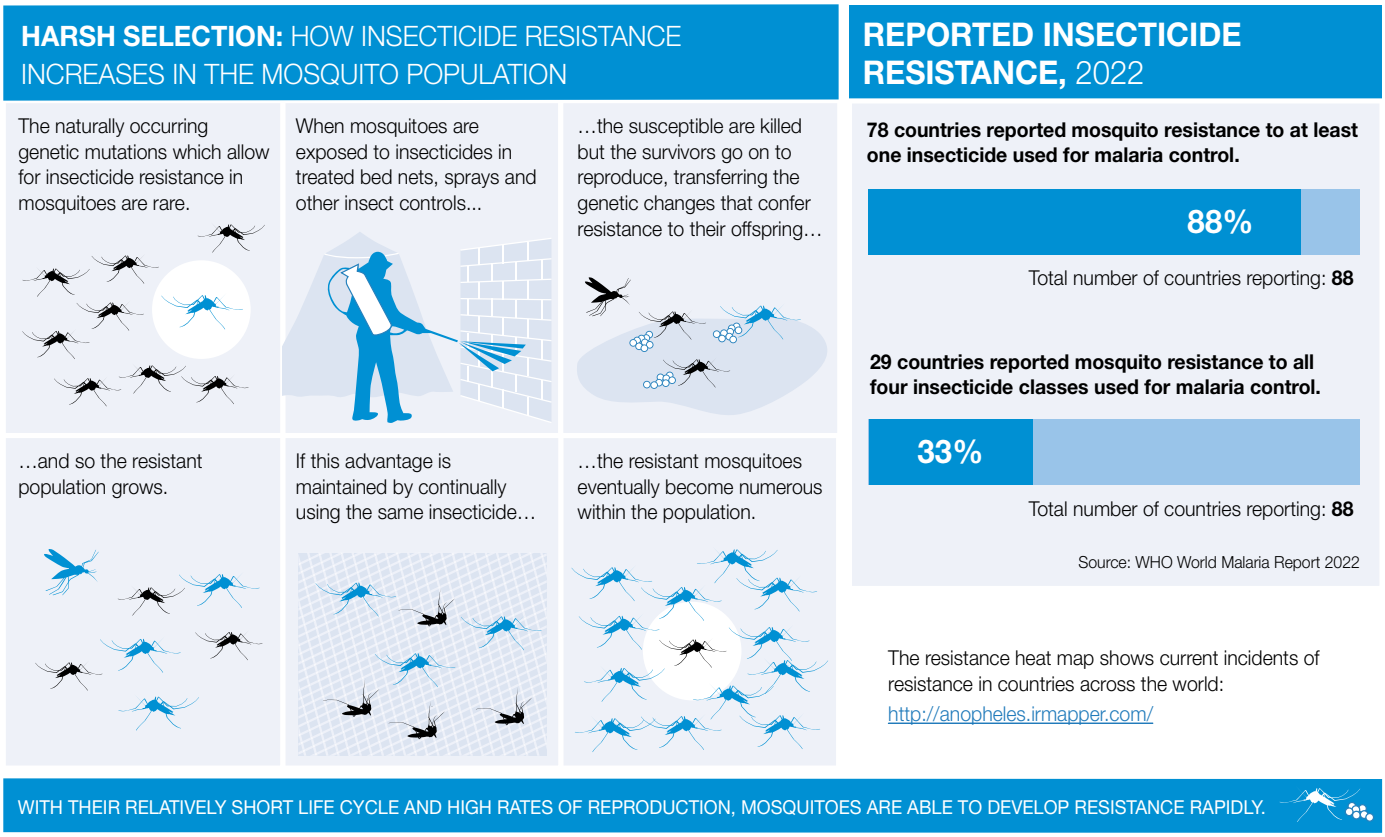
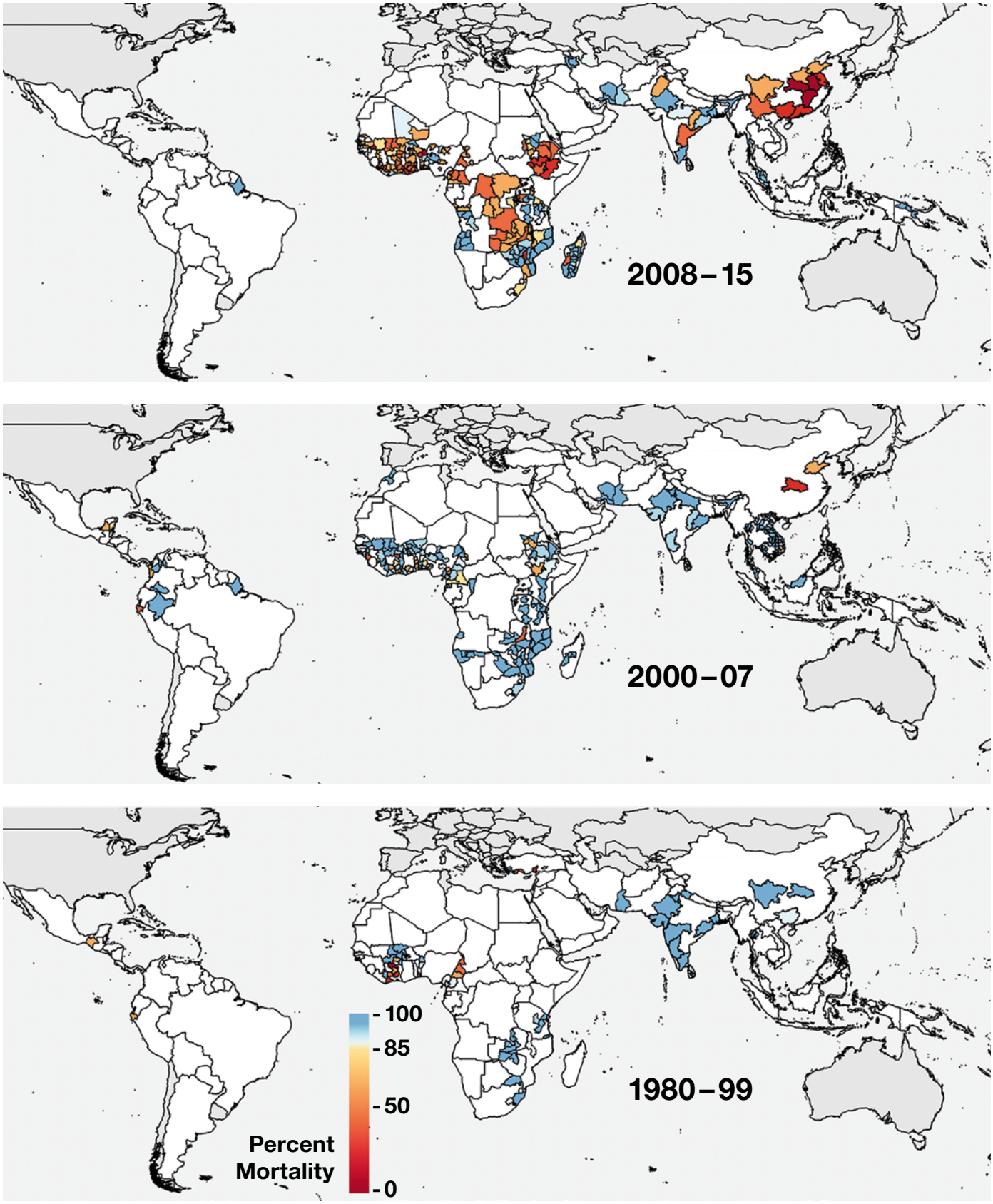


**Figure 2:** Trends in pyrethroid resistance for *Anopheles*[7]



# Chlorfenapyr – a new insecticide for vector control

Chlorfenapyr, a pyrrole, was launched by BASF Crop Protection division in 1995. It is registered in over 40 countries mainly for Pest Control use (e.g., US EPA approval for use in kitchens and food storage). It is listed in Group 13 in the IRAC MoA classification as uncoupler of oxidative phosphorylation via disruption of the proton gradient. Development work at BASF showed that it can be repurposed for the use in Public Health as a contact insecticide to control mosquitoes.

## Mode of Action of chlorfenapyr

Unlike other adulticides in vector control, chlorfenapyr is not neurotoxic. It owes its toxicity to the disruption of cellular respiration and oxidative phosphorylation in mitochondria[8]. Owing to its unique MoA, chlorfenapyr is active against insecticide resistant and susceptible mosquitoes. Evaluations performed on *Anopheles gambiae, Anopheles funestus, Anopheles arabiensis* and *Culex quinquefasciatus* mosquitoes show no cross resistance of chlorfenapyr to mechanisms that confer resistance to standard neurotoxic insecticides as organochlorines, pyrethroids, organophosphates and carbamates[9,10,11].

The MoA of chlorfenapyr and its effect as an insecticide requires several steps to take place. The first step is the metabolism of parent chlorfenapyr to the active drug. Chlorfenapyr is a pro-insecticide that is activated by cytochrome P450 monooxygenases to its active metabolite CL 303268.

This active metabolite then acts by disrupting the production of adenosine triphosphate (ATP) through oxidative phosphorylation in mitochondria of cells. It facilitates proton loss from the inside to the outside of the mitochondria via the inner mitochondrial membrane. When uncoupled from a proton energy source, the mitochondria are unable to generate ATP and the cells cease to function (Figure 4). Chlorfenapyr conversion rates from parent to drug are mitigated by biochemical, physiological, behavioral and environmental influencers that induce mortality ranging from 24 h up to 168 h post-exposures in mosquitoes. The speed and scope of conversion to its pro-insecticidal metabolite form will dictate its speed and relative mortality rates.

**Figure 3:** Chlorfenapyr metabolism of parent (left) to secondary metabolite (right)

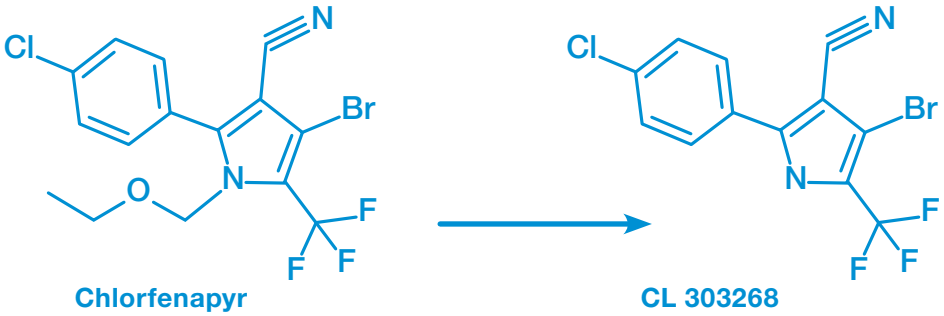
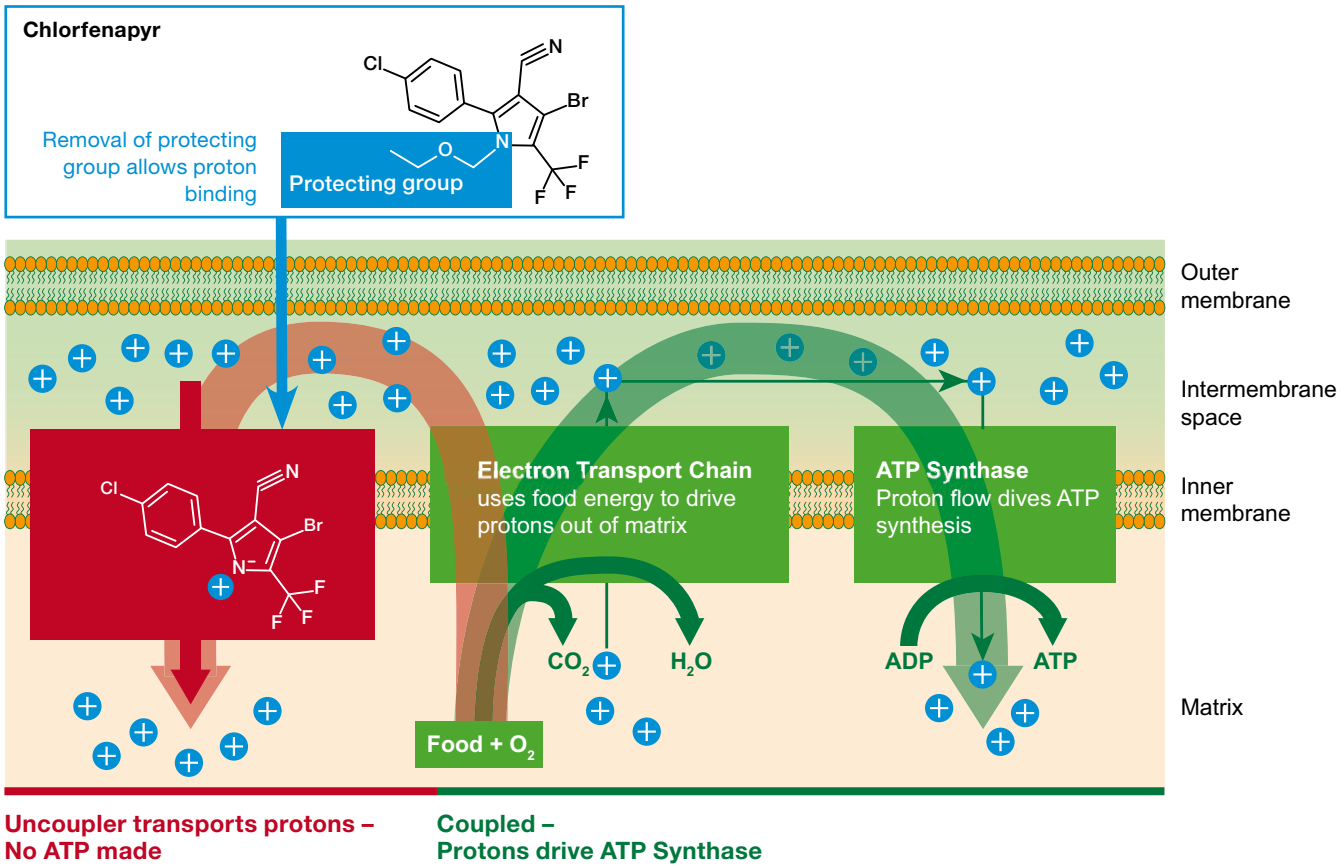


**Figure 4:** Chlorfenapyr inhibits ATP synthesis in mitochondria




It's important to note that piperonylbutoxide (PBO), a synergist used in other second-generation ITNs, is known to be an antagonist to parent chlorfenapyr. It blocks the P450 enzymes by which the chlorfenapyr is metabolized to the active metabolite[8]. PBO is an established antagonist.

## Effect of chlorfenapyr on plasmodium

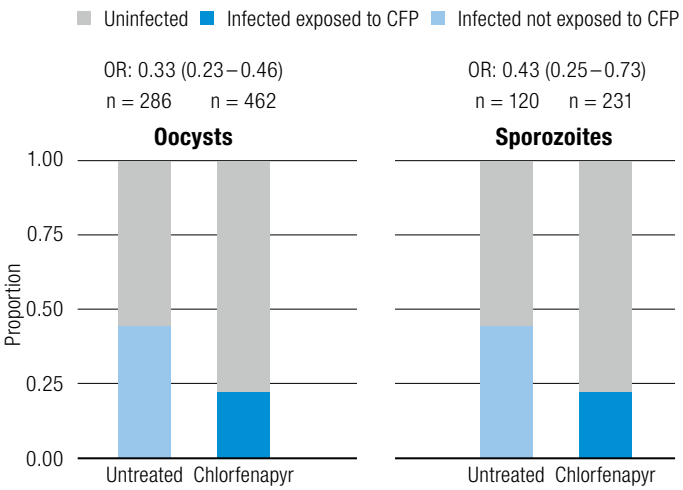
Plasmodium possess mitochondria, just like their mosquito vectors. There is potential for malarial infected mosquitoes to acquire doses from ITNs which may contribute either directly to mortality of Plasmodia or at least impair them to reduce transmission potentials. It was an established fact that the principal metabolite of chlorfenapyr through *n*-dealkylation was known to elicit lethal effects on plasmodium *in vitro*[12].

The effect of chlorfenapyr netting treated with 200 mg/m$^2$ to reduce malaria transmission was evaluated using a modified WHO tunnel test[13]. Pyrethroid-resistant *Anopheles gambiae s.s.* Kisumu with established Knockdown resistance *(kdr)* mosquitoes were exposed for 8 hours overnight. Exposed mosquitoes (to untreated control and chlorfenapyr treated netting) were provided with a gametocytemic blood meal from naturally infected individuals. Prevalence and intensity of oocysts and sporozoites were determined on day 8 and day 16 respectively post feeding.

The results in Fig. 5 demonstrate that chlorfenapyr substantially reduces the proportion and the intensity of Plasmodium-infected mosquitoes at sub-lethal doses and this will further decrease the occurrences of malaria in communities beyond the direct killing of mosquitoes.

This also partially explains the reductions observed in large-scale epidemiological trials of Interceptor® G2 nets that provided significant reductions in malaria transmissions through 2 years, and beyond (see Chapter “Epidemiological efficacy of Interceptor® G2”).

**Figure 5:** Proportion of *P. falciparum* infected mosquitoes with parasite intensity of oocysts and sporozoites following exposures to chlorfenapyr treated netting at 200 mg/m$^2$ chlorfenapyr in a modified WHO tunnel test; (OR were derived from a mixed-effects logistic regression analysis)




OR were derived from mixed-effects logistic regression

## Chemical and physical profile of chlorfenapyr

The chemical profile of chlorfenapyr is very similar to the one of alpha-cypermethrin, one of the pyrethroids used on ITNs. Both active ingredients are solid at room temperature (RT), similar in molecular weight and show a very low solubility in water which helps to retain the active ingredient up to 20 washes. The very low vapor pressure of both active ingredients is suitable to minimize loss during production and use.

**Table 1:** Chemical and physical profile of chlorfenapyr and alpha-cypermethrin

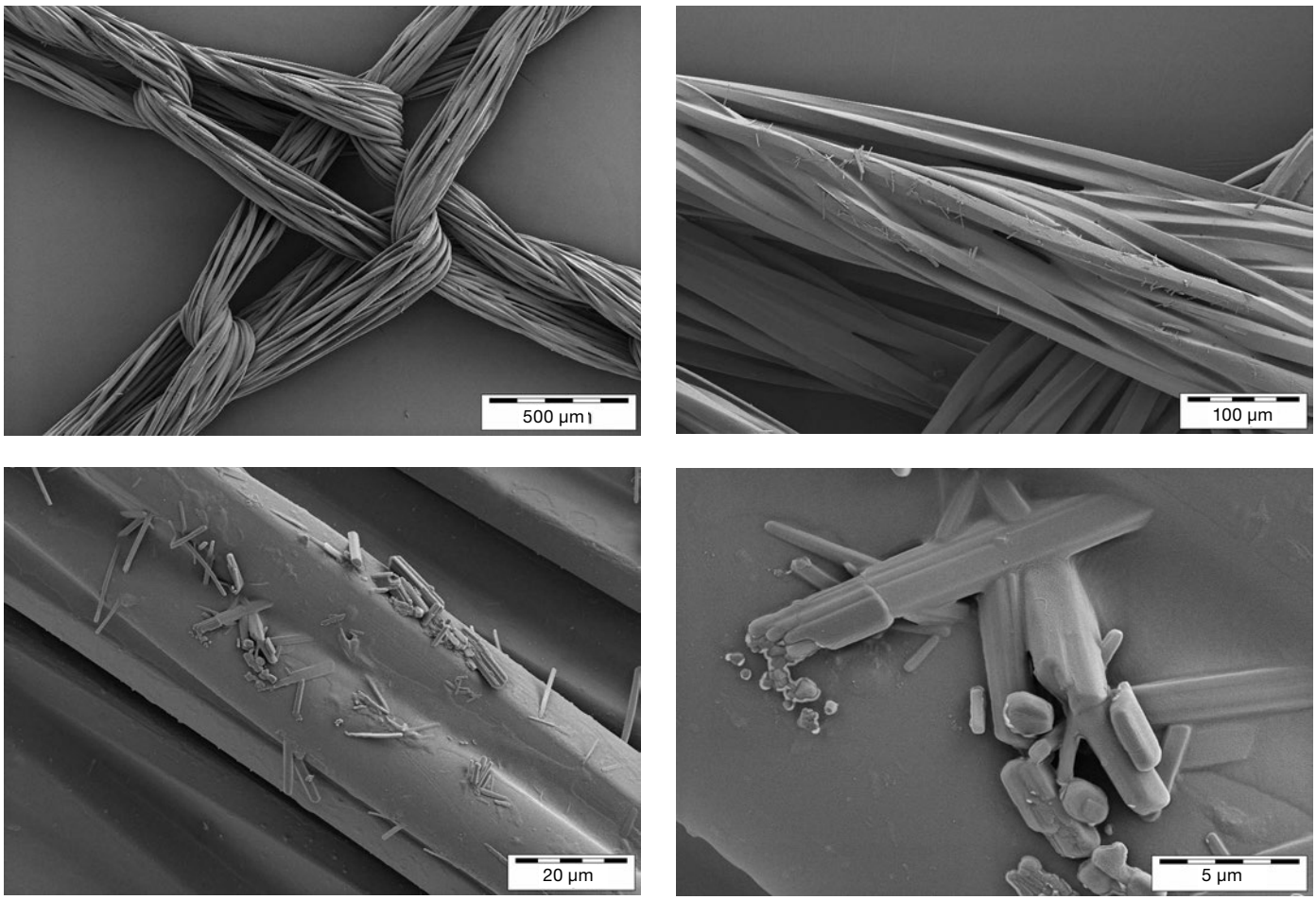
| | Chlorfenapyr | Alpha-Cypermethrin |
|---|---|---|
| Molecular weight [g/mol] | 407.6 | 416.3 |
| Physical state at RT | Solid, crystalline | Solid, crystalline |
| Melting point [°C] | 100 – 101 | 81 – 84 |
| Solubility in water @ 20 °C [mg/L] | 0.12 | 0.004 – 0.008 |
| Vapor pressure @ 25 °C [Pa] | 5.4 x 10-6 | 3.4 x 10-7 |

# Interceptor® G2 with chlorfenapyr and alpha-cypermethrin

Interceptor® G2 is the second-generation ITN developed by BASF with a combination of chlorfenapyr and alpha-cypermethrin to control insecticide resistant mosquitoes. Interceptor® G2 is a multifilament polyester net produced with a unique textile-finishing process developed by BASF´s textile technologists using a proprietary polymer system. It contains 200 mg/m$^2$ chlorfenapyr and 100 mg/m$^2$ alpha-cypermethrin.

On mosquito netting, chlorfenapyr is toxic to insecticide resistant and susceptible mosquitoes. It lacks the property of typical pyrethroid excito-repellency crucial for reducing mosquito biting rates and providing personal protection to net users[14]. In Interceptor® G2, the pyrethroid component, alpha-cypermethrin, provides excito-repellency and personal protection whilst the chlorfenapyr component restores insecticidal activity against insecticide resistant mosquitoes.

**Figure 6:** Scanning electron microscope images of Interceptor® G2 showing chlorfenapyr and alpha-cypermethrin crystals on netting fibers




Interceptor® G2 is the first ITN based on coated polyester (PET) with an active ingredient other than a pyrethroid with an established public health impact. To date, all newly developed nets with ingredients other than pyrethroids are using the technology of incorporating the ingredients in polyethylene fibers. The advantage of coating the active ingredient onto the surface is that it is readily available avoiding time consuming migration of the ingredients to the surface, commonly known as regeneration time (see also Figure 6). Consequently, the regeneration time for both ingredients have been found to be only 1 day[15]. Further, the stability of the PET fiber is not influenced by the coating, while incorporating ingredients into polyethylene fibers might weaken their strength.

The PET net Interceptor® G2 employs the same netting fabric that has been shown to be more favored over other net fabrics[16] thus enhancing user experiences and potential continued use of Interceptor® G2 throughout its lifetime.

# Epidemiological and biological efficacy of Interceptor® G2

## Epidemiological efficacy

This next-generation dual active ingredient ITN required an evaluation to demonstrate its effectiveness against malaria in human populations in areas characterized by different insecticide resistance intensities and major vector species. The ability to document the reduction in malaria demonstrates a Public Health Value (i.e., impact). Cluster randomised controlled trial (cRCT) data was employed to compare the effectiveness of the dual a.i Interceptor® G2 against pyrethroid-only ITNs (Interceptor®, 200 mg/m$^2$ alpha-cypermethrin). Both malaria prevalence and incidence in areas of documented pyrethroid insecticide resistance were reduced.

Beginning in 2019, nearly 40,000 Interceptor® G2 were distributed along with standard pyrethroid-only ITNs in Tanzania[17]; nets were also distributed in Benin in early 2020. In Tanzania Interceptor® G2 provided significantly better protection over two years than did pyrethroid-only ITNs: Children aged six months to 14 years had 55% lower odds of having malaria two years after the Interceptor® G2 distribution, and children aged six months to 10 years had 44% lower malaria incidence over the two-year period. After three years, a reduction of 43% was observed.

In Benin[18,19], a significant reduction in odds of malaria infection prevalence were detected in Interceptor® G2 compared to pyrethroid-only ITNs at six months (reduction of 53%) and 18 months (reduction of 39%) with a strong effect observed at six months. A 46% reduction of malaria incidence was observed.

The data available from both cRCTs demonstrated a significant impact of Interceptor® G2 on malaria prevalence compared to a pyrethroid-only ITN and surpassed the reduction targets for which they were originally designed.

Interceptor® G2 has demonstrated evidence of significant Public Health Value based on a clear protective effect as demonstrated in two cRCTs, encompassing different eco-epidemiological settings. From both public provider and donor perspectives, Interceptor® G2 is also the most cost-effective of the three dual active ingredient ITNs tested in the two RCTs.

**Table 2:** Malaria Infection prevalence* (intention to treat)

| Survey | Intervention | Tanzania[18] | | Benin[19] | |
|---|---|---|---|---|---|
| | | *Prevalence* | *Reduction* | *Prevalence* | *Reduction* |
| 6 months | Interceptor® | | | 28.0% | |
| | Interceptor® G2 | | | 15.7% | 53% |
| 12 months | Interceptor® | 31.2% | | | |
| | Interceptor® G2 | 15.6% | 53% | | |
| 18 months | Interceptor® | 52.3% | | 38.7% | |
| | Interceptor® G2 | 40.9% | 44% | 27.9% | 39% |
| 24 months | Interceptor® | 45.8% | | | |
| | Interceptor® G2 | 40.9% | 55% | | |
| 30 months | Interceptor® | 53.0% | | | |
| | Interceptor® G2 | 41.7% | 39% | | |
| 36 months | Interceptor® | 37.4% | | | |
| | Interceptor® G2 | 22.8% | 43% | | |

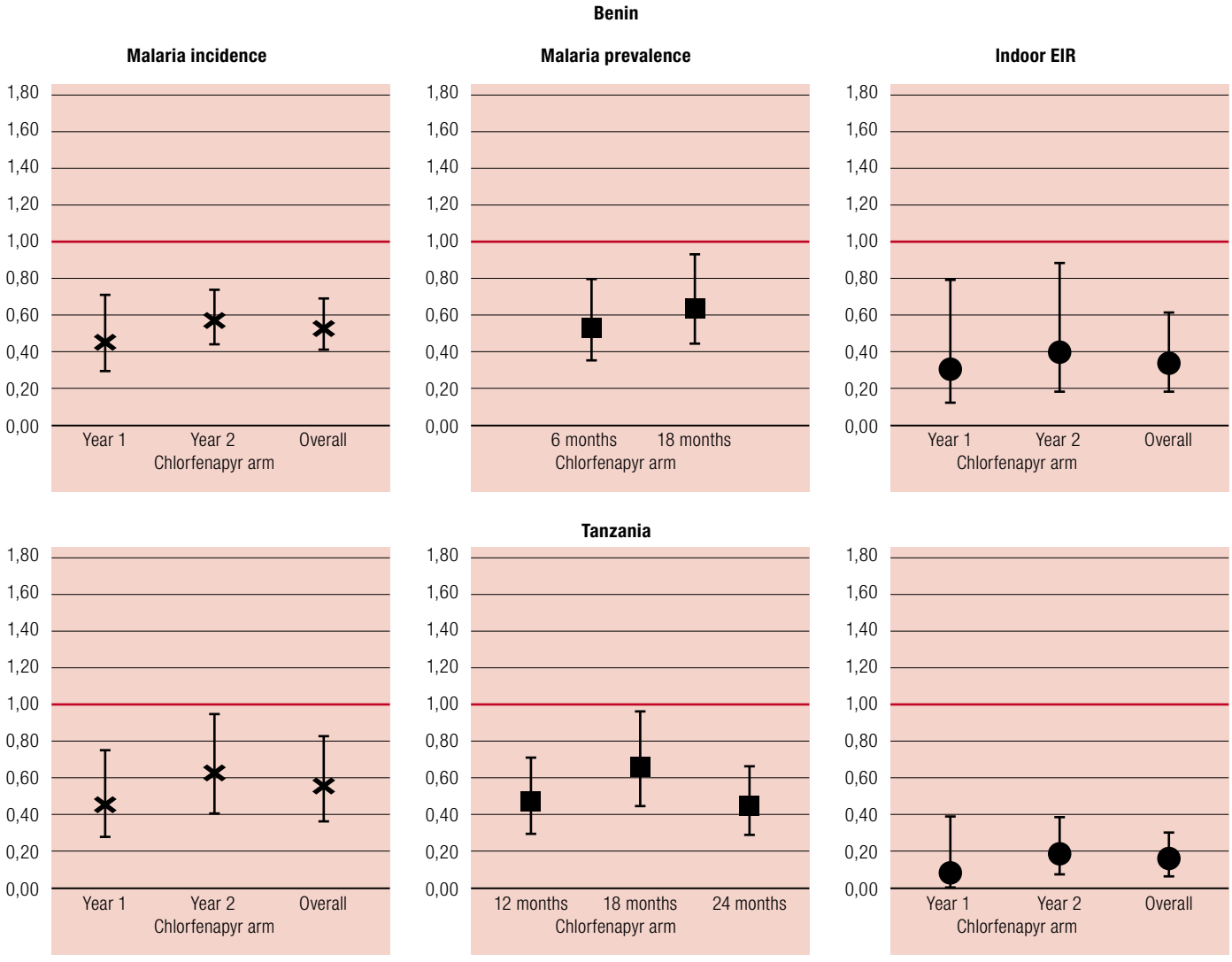
*** Malaria prevalence:** blood samples of every enrolled child will be tested for malaria using mRDTs

**Table 3:** Malaria incidents*

| Intervention | Tanzania[15] | | Benin[16] | |
|---|---|---|---|---|
| | *Incidence per child per year* | *Reduction* | *Incidence per child per year* | *Reduction* |
| **Overall (year 1 and 2 combined)** | | | | |
| Interceptor® | 0.46 | | 1.02 | |
| Interceptor® G2 | 0.23 | 44% | 0.56 | 46% |
| **Year 1** | | | | |
| Interceptor® | 0.32 | | 0.77 | |
| Interceptor® G2 | 0.13 | 54% | 0.35 | 54% |
| **Year 2** | | | | |
| Interceptor® | 0.57 | | 1.19 | |
| Interceptor® G2 | 0.31 | 49% | 0.69 | 43% |

***Incidence of malaria cases** (temperature ≥37·5°C or fever within 48 h and positive rapid diagnostic test) in children aged 6 months to 10 years

**Figure 7:** Comparison of results from the RCT in Tanzania and Benin
(Entomological inoculation rate (EIR): measure of malaria transmission intensity defined as the product of the human biting rate (HBR) and sporozoite infection rate (SIR))*




*Personal communication M. Accrombessi

## Biological efficacy

The presented experimental hut trials[20] (see table 4) use a similar design. One treatment arm contained an untreated net as negative control. Interceptor® nets with an active ingredientcontent of alpha-cypermethrin of 200 mg/m² on PET unwashed, as well as washed 20 times, were included as positive controls representing the standard pyrethroid-only ITN.

The purpose of keeping the design similar was to evaluate the vector control impact of Interceptor® G2 in settings in East and West Africa with different *Anopheles* species with varying resistance degrees and profiles.

**Table 4:** Overview on experimental hut trials

| Country | Location | Year | Nets tested | | | Target species | Status of insecticide resistance |
|---|---|---|---|---|---|---|---|
| | | | 0 W | 15 W | 20 W | | |
| Benin 1[21] | Cové | 2014 | ✘ | ✘ | ✘ | *An. gambiae* | *kdr* mutation + metabolic oxidases |
| Benin 2*[22] | Cové | 2015 | ✘ | | | *An. gambiae* | *kdr* mutation + metabolic oxidases |
| Burkina Faso[23] | Bama/Vallée du Kou | 2014 | ✘ | | ✘ | *An. gambiae* | *kdr* mutation + metabolic suspected |
| Tanzania[24] | Moshi | 2014 | ✘ | | ✘ | *An. arabiensis* | pyrethroid-resistant |
| Tanzania[25] | Muheza | 2015 | ✘ | | ✘ | *An. funestus* | pyrethroid-resistant |
| Tanzania**[25] | Muheza | 2016 | ✘ | | ✘ | *An. funestus* | pyrethroid-resistant |
| Ivory Coast**[26] | M'bé | 2016 | ✘ | | ✘ | *An. gambiae* | *kdr* mutation + metabolic; DDT, pyrethroid and carbamate resistance |
| Tanzania[27] | Ulanga District | 2020 | ✘ | | ✘ | *An. arabiensis* | pyrethroid-resistant |

* Unwashed Interceptor® G2 compared to IRS
** WHOPES Phase II trial

## First experimental hut trial in Benin[21]

The mortality of host-seeking *An. gambiae s.l.* exposed to the standard pyrethroid-only Interceptor® ITN was less than 25% (Figure 8). This low mortality is typical for pyrethroid-only ITNs evaluated in Benin, as the main vector species, *An. coluzzii* has developed high-level resistance to alpha-cypermethrin (200-fold) through a combination of L1014F kdr and CYP6P3 P450 mechanisms[28].

Interceptor® G2 restored the capacity of ITNs to control highly resistant populations of *An. gambiae s.l.* showing a corrected mortality of 71% when unwashed. The corrected mortality of 65% seen with the Interceptor® G2 after 20 washes shows that the formulation is wash resistant.

**Figure 8:** Mortality rates of wild, pyrethroid resistant *An. gambiae s.l.* in experimental huts with with untreated nets, Interceptor® ITN and Interceptor® G2 ITN

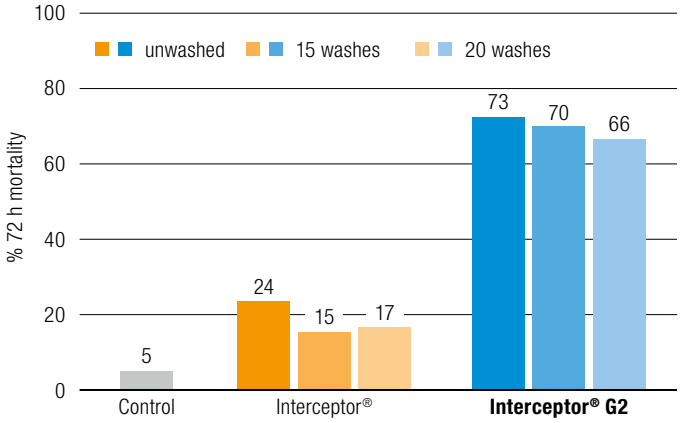
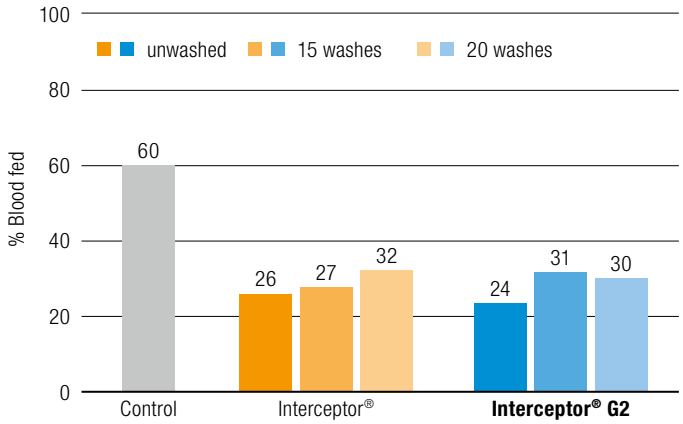



**Figure 9:** Blood feeding rates of wild, pyrethroid resistant *An. gambiae s.l.* in experimental huts with Interceptor®, Interceptor® G2 and untreated nets




Blood feeding of mosquitoes was 47–60% less with Interceptor® G2 and pyrethroid-only Interceptor® relative to the untreated net (Figure 9). There was no significant difference in blood feeding between Interceptor® G2 and Interceptor® over 20 washes. The alpha-cypermethrin component made an important contribution to blood feeding inhibition (BFI) and personal protection, as indicated by the similarity of response between the pyrethroid-only ITN and the mixture-based ITN.

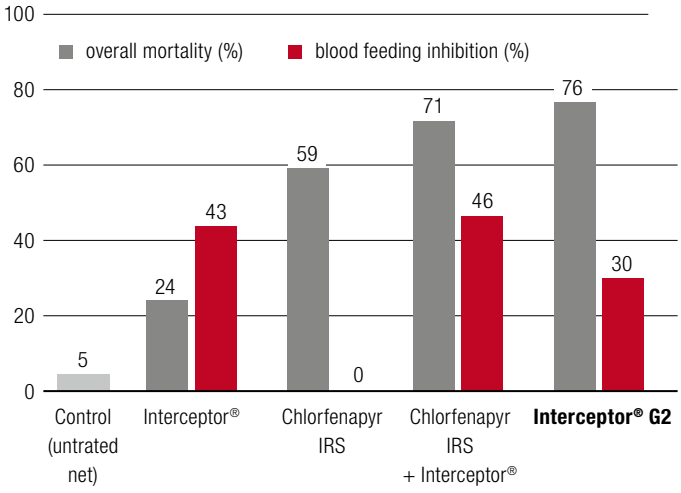
## Second experimental hut trial in Benin[22]

A second study was conducted at the Cové field station near Cotonou. The purpose of the study was to assess the efficacy of deploying a combination of unrelated insecticides against pyrethroid resistant populations of malaria vectors either as a combined non-pyrethroid IRS and pyrethroid-only ITN intervention or as a dual active ingredient ITN, such as Interceptor® G2.

The design included only unwashed Interceptor® and Interceptor® G2 nets. Additionally, one treatment arm was sprayed with chlorfenapyr IRS at a dose rate of 250 mg/m$^2$. Another arm contained a combination of IRS with chlorfenapyr at 250 mg/m$^2$ and pyrethroid-only Interceptor® ITN with alpha-cypermethrin (200 mg/m$^2$) (See Figure 10).

Interceptor® G2 and the combined use of chlorfenapyr IRS and pyrethroid-only Interceptor® provided comparable levels of improved control of insecticide-resistant malaria vectors. Where pyrethroid-only ITNs are being used, the addition of chlorfenapyr IRS is a viable strategy for improving control in high insecticide resistant settings.

**Figure 10:** Mortality and blood feeding inhibition of pyrethroid resistant *An. gambiae* in experimental huts in Cové, Benin




## WHOPES supervised Phase II trial in Ivory Coast[26]

The phase II WHOPES trial was carried out at M'bé in the north of Bouaké in central Côte d'Ivoire. Anopheline fauna in the study area are mainly *An. coluzzii* (formerly M molecular form of *An. gambiae s.l.*). that show resistance to organochlorides, pyrethroids and carbamates with an allelic frequency of the L1014F Kdr mutation around 80% and the presence of metabolic resistance mechanisms.[29]

**Figure 11:** Mortality rates of wild *An. gambiae* collected in experimental huts with treatments versus untreated control

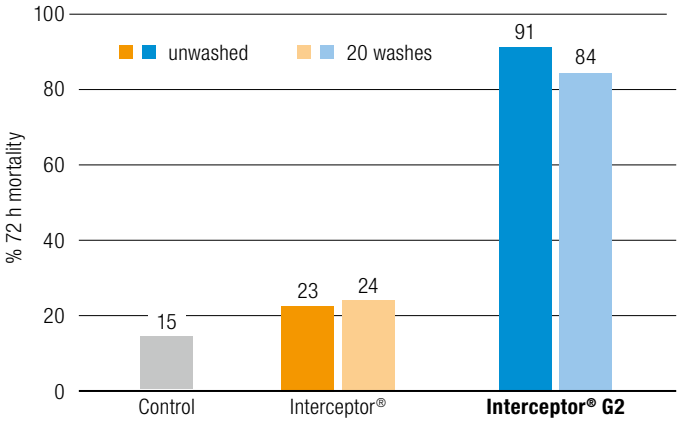
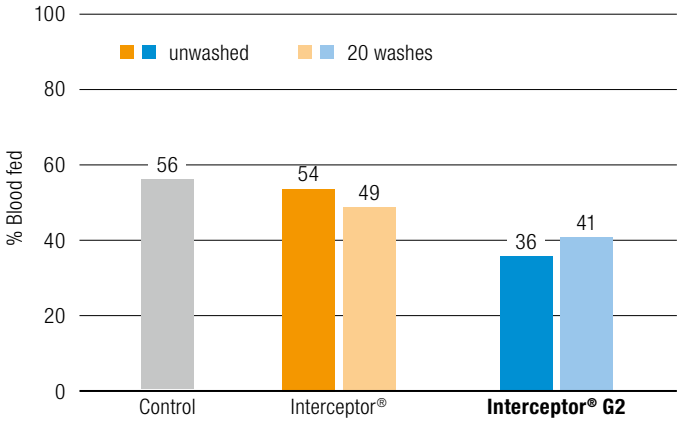



**Figure 12:** Blood feeding rates of wild *An. gambiae* collected in experimental huts with treatments versus untreated control




This study demonstrated that Interceptor® G2 provided better efficacy (mortality and BFI) against resistant *An. gambiae* than a reference pyrethroid-only Interceptor®, indicating that the active ingredient chlorfenapyr significantly impacted the ITN efficacy.

# What is so special about chlorfenapyr?

## Chlorfenapyr – a slow acting insecticide?

Unlike the pyrethroids and all other classes of insecticide currently recommended for adult mosquito control, the chlorfenapyr target site of activity is not the insect nervous system. Instead, chlorfenapyr, after being metabolized by P450 enzymes at the cellular level, acts by disrupting respiratory pathways and proton gradients through the uncoupling of oxidative phosphorylation within the mitochondria. Current WHO guidelines for identifying new insecticides and measuring toxic activity against malaria vectors are based on historic precedents established for neurotoxins, such as pyrethroids, organochlorines, carbamates, and organophosphates.

When applied to mosquito nets occupied by human volunteers in experimental hut trials, chlorfenapyr induces relatively high rates of mortality among host-seeking mosquitoes regardless of their insecticide resistance status as their metabolic state is elevated and the demand for energy is high. Yet, in some laboratory bioassays, such as the WHO cone test, chlorfenapyr appears slow acting or induces patterns or levels of mortality that are not typical of neurotoxic insecticides and are not predictive of mortality induced by chlorfenapyr-treated nets in hut trials.

These first observations in the laboratory led to generally applying a holding time of up to 72 h after exposure. Further evaluation showed that under field conditions, meaning when wild *Anopheles* are host-seeking during the night in experimental hut trials for example, the mortality observed after 24 h of holding is already very high.

Table 5 lists the mortality observed after 24 h and 72 h of holding in the experimental hut trials described in earlier chapters. The finding is that Interceptor® G2 kills about 70–97% of the total mosquitoes already after 24 h, comparable to the pyrethroid-only ITN Interceptor®.

**Table 5:** Mortality after 24 h vs 72 h holding period in experimental hut trials

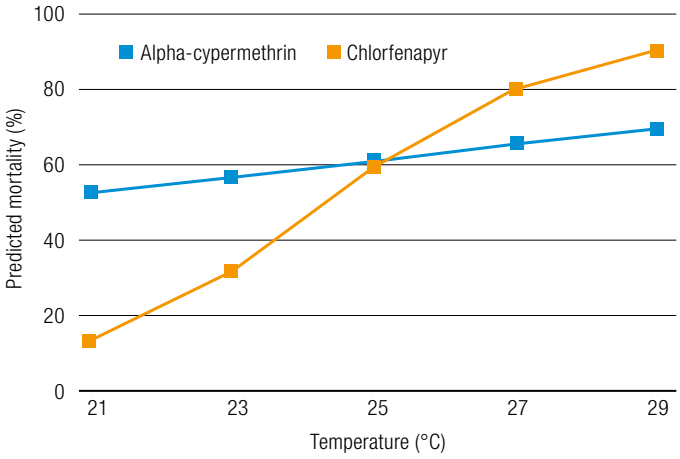
| Country | Mortality | Untreated | Interceptor® | | Interceptor® G2 | |
|---|---|---|---|---|---|---|
| | | | 0 W | 20 W | 0 W | 20 W |
| Burkina Faso[23] | 24 h | 10% | 25% | 18% | 78% | 74% |
| | 72 h | 11% | 28% | 21% | 80% | 78% |
| | % of mortality happening in the first 24 h | 85% | 91% | 89% | 97% | 95% |
| Benin 1[21] | 24 h | 3% | 20% | 13% | 61% | 54% |
| | 72 h | 5% | 24% | 17% | 73% | 66% |
| | % of mortality happening in the first 24 h | 67% | 84% | 78% | 84% | 81% |
| Benin 2[22] | 24 h | 2% | 11% | | 55% | |
| | 72 h | 5% | 24% | | 77% | |
| | % of mortality happening in the first 24 h | 50% | 44% | | 74% | |
| Moshi, Tanzania[24] | 24 h | 0% | 61% | 42% | 71% | 61% |
| | 72 h | 0% | 63% | 45% | 76% | 71% |
| | % of mortality happening in the first 24 h | | 97% | 93% | 93% | 86% |
| Muheza, Tanzania[25] | 24 h | 9% | 15% | 14% | 48% | 50% |
| | 72 h | 21% | 37% | 34% | 60% | 70% |
| | % of mortality happening in the first 24 h | 44% | 40% | 42% | 79% | 71% |

## Chlorfenapyr in Cone Bioassays

The metabolic state of the mosquitoes is crucial for the conversion of parent chlorfenapyr to its pro-insecticidal form. This metabolic state is influenced by the following parameters leading to higher mortality in lab bioassays:

- time of exposure
- time of holding
- temperature during exposure and holding time
- time of the test during day or night
- physiological state of the mosquito (host-seeking)

**Figure 13:** Predicted mortality of *An. gambiae* Kisumu by treatment between 21 and 29 °C[30]




*Anopheles* naturally searching for a host at night are in an elevated metabolic state. Chlorfenapyr demonstrates better performance under these conditions whereas laboratory tests during the day with mosquitoes in a sedentary or non-elevated metabolic state show more varying and lower mortalities.

Figures 14a and 14b present the proportions of pyrethroid-susceptible and resistant mosquitoes that were killed 72 h after a 3-minute exposure to insecticide-treated netting in WHO cone bioassay. On testing, unwashed netting against the pyrethroid-resistant Cové strain, mortality did not exceed 12% with any of Interceptor® and Interceptor® G2.

Figures 15a and 15b show the proportions of pyrethroid-susceptible and resistant *An. gambiae* killed 72 h after exposure to the same pieces of insecticide-treated netting in overnight tunnel tests. Tests against the pyrethroid resistant Cové strain recorded 22% mortality with the unwashed pyrethroid-only Interceptor® net and 82% with the unwashed Interceptor® G2.

Comparing the laboratory bioassay results on the pyrethroid resistant strain with the experimental hut results on the pyrethroid-resistant wild population, the tunnel test was the better predictor of hut mortality than was the cone. The mortality with unwashed Interceptor® G2 was 5% in the cone, 82% in the tunnel test and 72% in the hut.

**Figure 14:** Mortality rates of *An. gambiae* in cone tests performed in Benin[18] with 3 min exposure to Interceptor® G2 and other nets.
(A) Susceptible Kisumu strain. (B) Resistant Cove strain

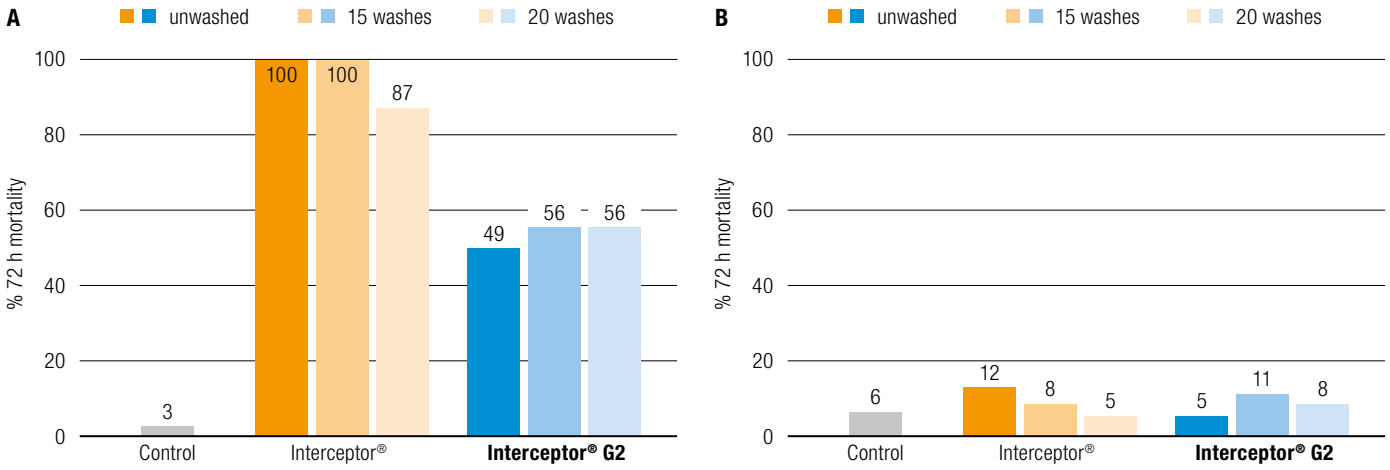



**Figure 15:** Response of *An. gambiae* in tunnel tests performed in Benin[21] with Interceptor® G2 and other nets.
(A) Mortality of susceptible strain. (B) Mortality of resistant strain

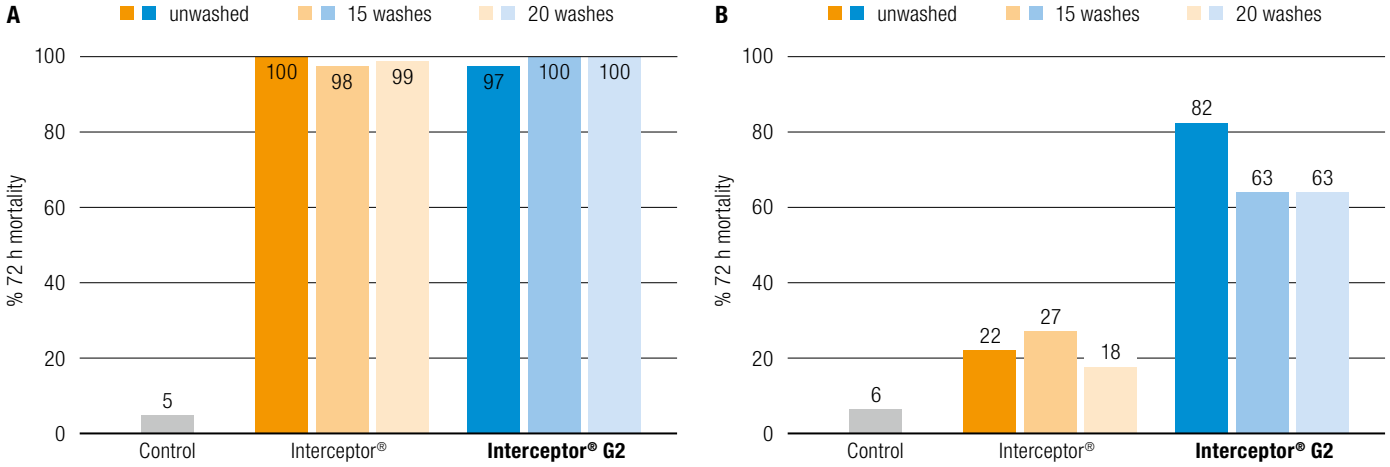
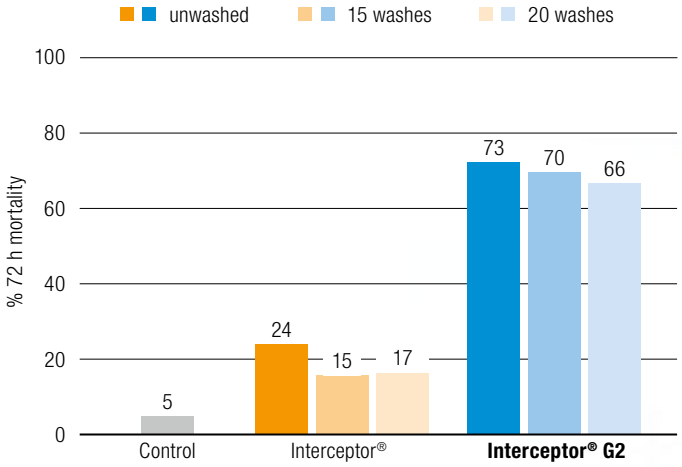



**Figure 16:** Experimental huts trials against wild, pyrethroid resistant *An. gambiae s.l.* with untreated nets, Interceptor® ITN and Interceptor® G2 performed in Benin[21]



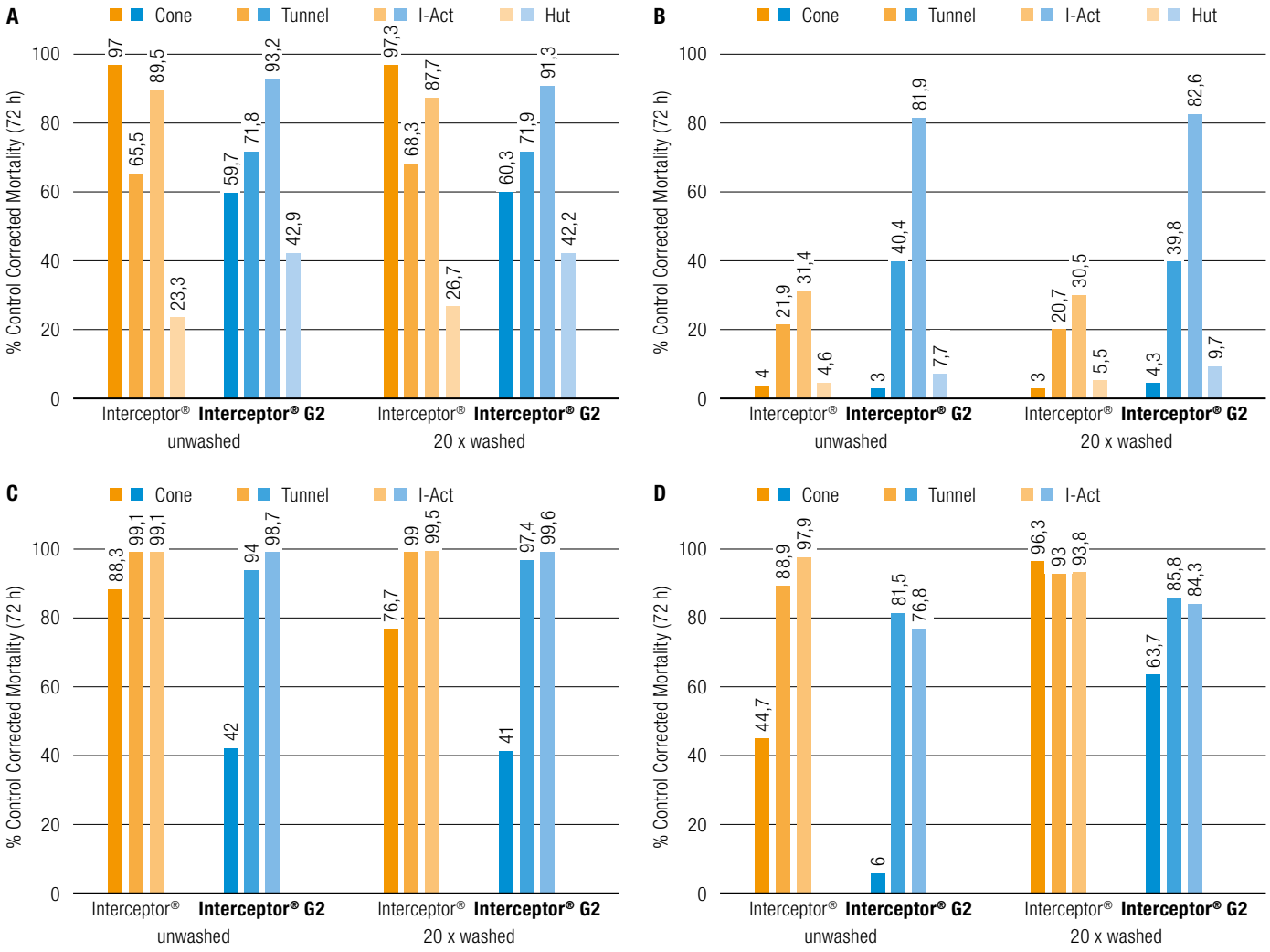
## Chlorfenapyr in “free-flying” laboratory bioassays

The WHO tunnel test is a well-established bioassay. However, it tests only a sample of a net and is therefore only able to accurately measure the chemical durability of an ITN and not the physical durability. In addition, it requires a high number of mosquitoes (100 per replicate).

The Ifakara ambient chamber test (I-ACT)[24] is designed to be a bridging bioassay that reproduces a more natural interaction between the mosquito and the human hosts beneath a bed net. The I–ACT makes use of whole nets and human hosts to evaluate bioefficacy of field-used ITNs, but the assay is done under controlled conditions with laboratory-reared mosquitoes. Mosquitoes are released into net chambers within which the test net is hung with a volunteer sleeping beneath, and all mosquitoes are recaptured in the morning. The use of laboratory mosquitoes (rather than conducting experimental hut trials with wild mosquitoes) is done to improve the precision of estimates by releasing mosquito cohorts of a defined number of mosquitoes with high recapture rate (99%) at the conclusion of exposure intervals.

Interceptor® G2 and pyrethroid-only Interceptor® were evaluated to compare the performance of each assay for durability monitoring of pro-insecticidal ITNs. In this evaluation, the I-ACT consistently predicted the results of experimental hut tests, measured with a similar magnitude of difference as a tunnel test and provided high-throughput and precise estimates of whole ITN protective efficacy. As a “free-flying” lab bioassay, it is especially suitable to evaluate products containing chlorfenapyr. The I-ACT is a recently recognized method approved by the WHO. Against resistant strains, superiority of Interceptor® G2 over pyrethroid-only Interceptor® was observed in all “free-flying bioassays” (see Fig.17).

**Figure 17:** Mosquito mortality after exposure to Interceptor® and Interceptor® G2 ITN in I-ACT, tunnel test, cone and experimental hut
A *An. arabiensis* (resistant), B *Cx. quinquefasciatus* (resistant), C *An. gambiae s.s.* (susceptible), *D Ae. aegyptii* (susceptible)[27]



## Discriminating concentration for chlorfenapyr

Discriminating concentrations (DC) are crucial for the monitoring of the resistance status of mosquito populations in vector control. In anticipation of Interceptor® G2 being distributed in sub-Saharan Africa, testing was conducted by the US President's Malaria Initiative (PMI) VectorLink project to develop a chlorfenapyr susceptibility bioassay protocol and gather baseline susceptibility information in field populations of mosquitoes[31,32,33,34,35]. A modified bottle bioassay protocol, based on the CDC bottle assays[36], was developed (1 h exposure time, 72 h holding time). The tests were performed between 2017 and 2020 at a time when nearly no usage of pyrrole insecticides could be found in sub-Saharan Africa for agricultural pest control.

Large-scale testing using 100 µg active ingredient/bottle with wild *An. gambiae s.l.* in 16 countries showed that this concentration was generally suitable with a median mortality rate of 100% at 72 h. There were many outliers when mortality was < 98%, indicating that 100 µg active ingredient/bottle may not be a suitable discriminating concentration. Tests conducted with 200 µg active ingredient/bottle in 10 countries produced similar trends to the 100 µg concentration but indicated that the 200 µg active ingredient/bottle concentration is likely to produce fewer cases of false resistance reporting than with 100 µg active ingredient/bottle.

Results of this large-scale testing also have shown that pyrethroid-susceptible colony strains are killed at lower concentrations than wild *An. gambiae s.l.* As a consequence, a DC developed only based on susceptible colonized strains would lead to a DC too low for field strains and false resistance reporting.

The activation of chlorfenapyr and its toxic action of disrupting cellular respiration, being metabolic processes, are both temperature dependent (see paragraph on MoA). The WHO-recommended temperature range of 27 °C ± 2 °C and relative humidity of 75% ± 10% essential for successful testing. To minimize the occurrence of false resistance reporting, tests should always be conducted in parallel with a well-characterized colony strain to try and detect issues with under-dosing or low testing temperature.

The data generated by the PMI VectorLink project were included in the multi-centre study conducted by WHO in 2017–2021[37]. One of key outcomes of the study was the development and validation of a new standard bottle assay procedure, "the WHO bottle bioassay", for testing compounds with modes of action that are not suitable for impregnation on filter paper – such as chlorfenapyr.

Chlorfenapyr was tested on *An. gambiae, An. stephensi, An. funestus* and *An. albimanus* resulting in a recommendation for DC of 100 µg/bottle at 72 h holding time. At the third WHO consultation in 2020- in view of the technical difficulties encountered in bottle bioassays with chlorfenapyr, specific instructions and guidance have been defined for monitoring insecticide resistance in wild mosquito populations in the field.

**The following instructions are given in the SOP for bottle bioassays[38].**

WHO bottle bioassays with chlorfenapyr have shown some interlaboratory variability in test results due to the strong influence of testing conditions (especially temperature during bioassays). Therefore, to confirm resistance to chlorfenapyr in a wild vector population, at least 3 WHO bottle bioassays need to be conducted with the same vector population. Furthermore:

- temperature should be kept within 27 °C ± 2°C and relative humidity within 75% ± 10% during all 3 tests;
- the mortality of test mosquitoes 72 hours post-exposure should be <90% in all 3 tests; and
- the mortality in the susceptible laboratory colony, tested in parallel to the wild mosquitoes, should be ≥98% in all 3 tests.

## CIPAC Method

CIPAC method 454/LN/M2/- and 570/LN/M/-. Determination of alpha-cypermethrin and chlorfenapyr in long-lasting insecticidal nets (ITNs)[39] is one of the first Collaborative International Pesticides Analytical Council (CIPAC) methods established for a mixture of a.i.´s. Typically CIPAC opposes to methods for mixtures to keep the number of methods manageable. The CIPAC method to analyze Interceptor® G2 was developed to determine the content of both a.i. in one injection to the gas chromatography (GC) apparatus to reduce variability in a.i. content and also to save time. Pieces of Interceptor® G2 were sampled according to WHO Guidelines[17], extracted with acetonitril and analyzed by GC. GC is preferred over high-pressure liquid chromatography (HPLC) as the GC method provides higher sensitivity. The new CIPAC method was validated in a small-scale trial with 5 laboratories and a full-scale trial with 18 participants. The method was published 2021.

# Why use Interceptor® G2?

## Superior Technology

The patented textile-finishing process and the polyester net coating process ensures that the Interceptor® G2 nets are odorless, soft to the touch and pleasant to sleep under. As the active ingredients are coated on the outside of the fibers it is readily available and no heat induced migration of the active ingredients from the inside of the fiber to the surface of the net is needed. The net needs no regeneration time and can be used in less than a day after washing. As no active material is incorporated into the fiber, the fiber preserves its originally designed strength. The patented polymer binder system ensures that only low depletion of the active ingredients from the surface takes place due to washing thus making the net long-lasting. Interceptor® G2 remains effective even after 20 washes.

## Safe to use

Chlorfenapyr has been used for pest control in kitchens and food storage since its launch in 1995. In Interceptor® G2, the pyrethroid component – alpha-cypermethrin – provides excito-repellency and personal protection whilst the chlorfenapyr component provides insecticidal activity against insecticide resistant mosquitoes.

The assessment of risk to humans of washing and sleeping under the Interceptor® G2 LN following the WHO Generic Risk Assessment Model for insecticide-treated nets[40] on behalf of WHO concluded that when used as instructed, Interceptor® G2 is safe and poses no risk to human health.


## Effective tool to control insecticide resistant mosquitoes

In contrast to the second-generation mosquito nets containing a combination of a pyrethroid with the synergist PBO, Interceptor® G2 provides a new non-pyrethroid active ingredient, chlorfenapyr. A synergist works by enhancing the effect of the pyrethroid by inhibiting the metabolic enzyme defense systems of the mosquito, but at the end, uses the same mode of action as a pyrethroid alone. The mode of action of chlorfenapyr is new to the control of mosquitoes. In experimental hut trials, Interceptor® G2 restored the control of highly resistant mosquitoes killing them as fast as a pyrethroid-only LN. It is highly effective in areas with high insecticide resistance as for example several West African countries as shown in the two RCT in Tanzania[18] and Benin[19].

## Innovative Active Ingredient System

Interceptor® G2 is coated with an innovative mixture of alpha-cypermethrin and chlorfenapyr. Chlorfenapyr is the first non-pyrethroid adulticide employed on a long-lasting mosquito net. Chlorfenapyr offers a new mode of action and thus shows no cross resistance to other insecticide classes used in vector control.

## Effective tool to reduce malaria

Interceptor® G2 was evaluated in comparison to the pyrethroid-only net Interceptor® in two large epidemiological trials in Tanzania and Benin. A 44% reduction of malaria incidence in Tanzania and 46% in Benin was observed for Interceptor® G2 over a period of 2 years.

# Technical information

## Product description

**Net material:** Polyester fibers (multifilament) coated with two insecticides, consisting of 100 Denier. For easier identification of the mixture net, dark threads can be knitted into the netting in a spacing of 5 cm giving a striped appearance.

**Shape:** Rectangular or conical

**Odor:** Odorless

**Appearance of insecticides on net:** Invisible

**Wash resistance:** Nets are manufactured to provide sufficient insecticidal efficacy for more than 20 washes.

**Storage stability:** In storage test, net material contains >95% of the original active ingredientcontent after 2 weeks at 54 °C.

**Handling precautions when using:** Interceptor® G2 can be repeatedly washed and still retains its efficacy (even after 20 washes) against malaria mosquitoes, if the following instructions are followed:

- Do not wash in a washing machine
- Do not use bleaching agents
- Wash without brushing, in tepid water, in a bowl with a small amount of soap
- Always dry in open air, in the shade
- Do not use an electric tumble dryer
- Do not iron
- Always keep Interceptor® G2 in the shade
- Do only use as bed net
- Do keep away from animals
- Do keep away from water bodies

The active ingredients used to treat this net are safe to use. However, in the unlikely event that someone experiences skin and eye irritation, wash the skin with mild soap and water and flush eyes with copious amounts of water. Wash the net before using the net again. Rinse your Interceptor® G2 mosquito net with water before first use to avoid possible skin irritation.

**Packaging:** Interceptor® G2 nets are individually packed in polyethylene bags with clear product identity indications to avoid confusion with other insecticide-treated nets.

**Care tag:** A care tag is stitched to each net. This label contains the washing instructions in short form on one side. On the other side information on net descriptors like size, the manufacturing and expiry date as well as an identification number is given. Additionally, three-dimensional barcodes allow to trace back every single net and connect it with the respective quality assurance data.

**Quality:** The quality and reliability of Interceptor® G2 nets is backed by advanced technology developed by BASF. Interceptor® G2 is an in-line, factory treated net, ensuring consistent quality and is subject to the same rigorous BASF quality control standards to which all products are adhered to.

Development, marketing, and sales, as well as the production sites, are ISO certified to comply with the requirements of the International Standard for Quality Management.

**Disposal:** When the useful life of the net is finished, Interceptor® G2 nets will not require any special handling. They should be disposed of according to protocols established by international organizations and local regulations for all ITNs.

**Risk assessment:** The two active ingredients of Interceptor® G2, alpha-cypermethrin and chlorfenapyr, show different toxic actions on different target organs and are therefore considered to act independently via simple additivity of effects.

BASF evaluated the potential human safety issues of sleeping under Interceptor® G2 nets using the WHO Generic Risk Assessment Model for insecticide-treated nets[41]. This model addresses risk for newborn babies, small children and adults sleeping under treated nets.

Worst-case criteria were used in conducting the assessment:

- Assumes a baby or child sleeps 12 hours under the bed net and would suck continuously on the netting
- A 12-hour continuous contact of skin with the netting via sweat is assumed
- Extraction data from unwashed, newly produced bed nets with artificial saliva were used

The results clearly show that systemic exposure is negligible. It can be concluded that no unacceptable risk occurs for newborn babies, children or adults when sleeping under Interceptor® G2 nets.

**Ecotoxicology:** Exposure of non-target organisms to alpha-cypermethrin and chlorfenapyr on the nets is highly unlikely when used in accordance to the recommendations. Washing of nets in natural water sources, such as rivers, streams, lakes, and dams, should be avoided.

## Specification

| Item | Criteria | Value / Limits | Dimension | Specified Norm |
|---|---|---|---|---|
| Active Ingredient (chlorfenapyr) | Total A.I. content | 200 ± 25% | [mg/m²] | 454/LN/M2/- and 570/LN/M/ |
| Active Ingredient (alpha-cypermethrin) | Total A.I. content | 100 ± 25% | [mg/m²] | 454/LN/M2/- and 570/LN/M/ |
| Mechanics Net Material | Warp knitting | – | – | ISO 8388 |
| | Yarn | 100% polyester, 100 Denier, minimum 32 filaments | – | ISO 2060, 1833 |
| | Mesh | Minimum 156 (24) | [per inch²] ([per cm²]) | ISO 7211/2 |
| | Area weight | 100 Denier: 40 ± 10% | [g/m²] | ISO 3801 / DIN EN 12127 |
| | Shrinkage | < 5% | [%] | ISO 5077, 6330/8A |
| | Bursting strength net | 100 Denier: ≥ 405 | [kPa] | ISO 13938-2 |
| Fire Safety | Flammability | Class 1 | – | CFR 1610 |

## Active ingredients of Interceptor® G2

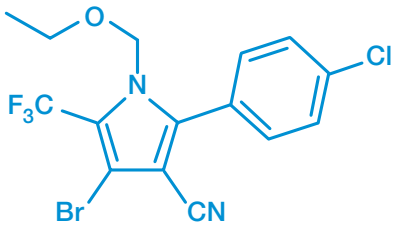
### *Chlorfenapyr*

**IUPAC:** 4-Brom-2-(4-chlorphenyl)-1-ethoxymethyl-5-trifluor-methyl-pyrrol-3-carbonitri

**Chemical Group:** Pyrroles

**IRAC Mode of Action Classification:** Group 13 – Uncouplers of oxidative phosphorylation via disruption of proton gradient

**Structural formula:**




*Empirical formula $C_{15}H_{11}BrClF_3N_2O$*
*Relative molecular mass 407, 61 g/mol*
*CAS Registry number 122453-73-0*
*CIPAC number 570*

**WHO specification:** The product fulfils the WHO specification 570/TC

**Target dose rate on Interceptor® G2:** 200 mg/m²

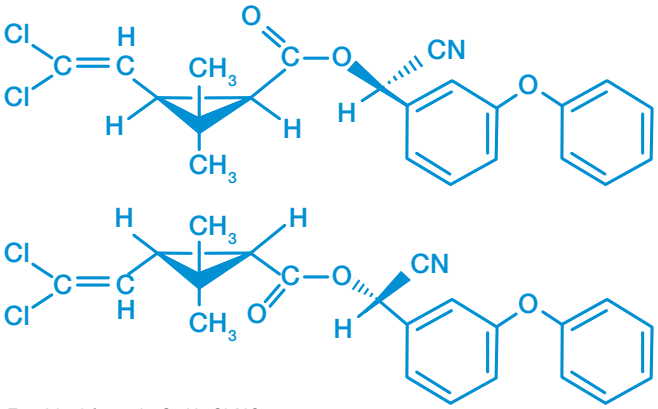
### *Alpha-Cypermethrin*

**IUPAC:** A racemic mixture of: (S)-a-cyano-3-phenoxybenzyl-(1R,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (R)-a-cyano-3-phenoxybenzyl-(1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

**Chemical Group:** Pyrethroids

**IRAC Mode of Action Classification:** Group 3 – Sodium channel modulators

**Structural formula:**




*Empirical formula $C_{22}H_{19}Cl_2NO_3$*
*Relative molecular mass 416.3 g/mol*
*CAS Registry number 67375-30-8*
*CIPAC number 454*

**WHO specification:** The product fulfils the WHO specification 454/TC

**Target dose rate on Interceptor® G2:** 100 mg/m²

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August 2023

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