



# Progress in Eliminating One-Year Dog Studies for the Safety Assessment of Pesticides

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**Abstract.** We reviewed six key peer-reviewed publications that assessed the need for one-year studies of pesticide toxicity in dogs. Each of the six papers took a different approach to comparing the value of one-year studies relative to three-month studies, and despite the adoption of different databases and approaches, each study reached the same conclusion: the recommended limit to the testing of pesticide toxicity in dogs should be three months.

Therefore, the present review supports the conclusion that the routine inclusion of a one-year dog study should not be a mandatory requirement for the safety assessment of pesticides, since it is scientifically no longer justifiable. We recommend that the OECD should adapt a harmonized approach that is in line with the legislation in Europe and the USA.

**Keywords:** Safety testing of pesticides · Regulatory testing · Dog studies  
Length of studies · NOAEL

## Introduction and Objective

Assessment of user safety and consumer safety is a key element in the development of crop protection products and their active ingredients. Conventionally, toxicity tests using laboratory animals have been the standard means for assessing potentially hazardous effects of the chemicals used in drugs, pesticides, and consumer products like food and feed. Testing in animals has long been criticized, and the publication in 1959 of Russell and Burch's Three Rs (Russell and Burch 1959) laid the groundwork that eventually led to the banning of animal tests for the safety assessment of cosmetics in the EU (EU Commission 2009a). Moreover, since safety testing using monkeys and companion animals, such as cats and dogs, has always been the target of criticism, scientists tend to avoid using these species in testing for regulatory purposes. Consequently, although safety studies using dogs are still conducted for pesticides and drugs, they are no longer mandatory for other consumer products. Therefore, my colleagues and I at the German Federal Institute for Risk Assessment (BfR) have tried to assess

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whether or not dog studies are a truly necessary means for the safety assessment of pesticides, and if they are, which types of dog studies should be used.

For the registration of pesticides repeat-dose studies with rodents and dogs have been essential elements for more than 50 years. According to international (OECD, EU) and national (US EPA and many others) test guidelines 90-day and one-year oral studies in rodents and dogs are the established standards for evaluating toxicity of pesticides. Testing typically consists of initial exploratory studies across a range of different concentrations to establish a dose that is then used in the three-month and one-year toxicity studies. Since at least 70 dogs are used to test each new chemical, and dozens of new chemicals are tested each year, the total number of animals needed quickly reaches the thousands. In recent years, changes to regulatory requirements have eliminated the need for one-year dog studies in the EU (EU Commission 2009b), and they are now required in the US, Canada, (Health Canada PMRA 2016; Linke et al. 2017) and Australia only when it can be demonstrated that dogs are more sensitive than rodents in 90-day studies.

Nevertheless, South Korea, Japan, and other countries still require a one-year dog study before a product can be approved, and this means that companies must conduct the study to be able to market the product in those countries, irrespective of the fact such testing is not required elsewhere.

The purpose of this review is to critically evaluate the need for three-months and one-year dog studies of toxicity and in particular to determine the importance, which of each of these dog studies has for the safety assessment of pesticides.

## **Review of Regulatory Data not in the Public Domain**

For more than 50 years a three-months and a one-year dog study have been mandatory for the global registration of pesticides. It is the purpose of the studies is to identify the dose at which no adverse effects occur, this is the “no observed adverse effect level” (NOAEL), which is then used for setting a safe reference dose for humans in order to enable a risk assessment.

The toxicity data used in safety studies is obtained from testing performed by private enterprise and submitted to regulatory agencies in confidential reports. In other words, they are not in the public domain and cannot be readily obtained for other scientific purposes, such as evaluating the extent to which dog studies are actually necessary for determining a NOAEL. And in spite of the fact that such evaluations important for scientific, animal welfare, and economic purposes, proprietary toxicity data cannot be obtained or used for such purposes without the consent of the owners of the reports, e.g., agrochemical companies.

As a regulatory scientist at the Federal Institute for Risk Assessment (BfR) in Germany, which is also the national agency for the regulation of pesticides, I was able to request permission from the owners of such data and from my colleagues in the pesticides administration of the BfR to conduct an evaluation of the extent to which dog studies are necessary to the safety assessment of pesticides. In order to protect the confidentiality of the data, the chemicals had to be coded for use in the study. Although the same data is held in the files of regulatory agencies in all EU member states, Japan,

and the US EPA, proprietary data on pesticides had never before been used for this type of study. In fact, the only agency that later followed our example and conducted a similar study was the US EPA. Consequently, there are only the three studies from our group at the BfR in Germany (Gerbracht and Spielmann 1998; Box and Spielmann 2005; Spielmann and Gerbracht 2001) and the three studies from the USA, in which the EPA was engaged (Baetcke et al. 2005; Doe et al. 2006; US 2006). Together with the 232 pesticides we analyzed in the German studies, the US EPA studies included both these same 232 chemicals and roughly 150 additional ones, which suggests that dog studies have been conducted for approximately no more than 380 chemicals. Unfortunately, not all the reports submitted for regulatory purposes included data from rodent studies, which would be a prerequisite in order to determine the NOAEL for pesticides using long-term rodent studies alone or by combining long-term rodent studies with short-term dog studies, rather than just long-term dog studies.

## Results of the Studies Conducted in Germany

The results of the safety reports submitted to the BfR in Germany for 232 pesticides (Gerbracht and Spielmann 1998; Spielmann and Gerbracht 2001; Box and Spielmann 2005) provided two major conclusions:

1. The testing of pesticides in dogs is indeed necessary because the dog has proved to be the most sensitive species for about 15% of the compounds examined.
2. Chronic studies are of limited value, since they provide essential information that cannot be obtained in sub-chronic studies only in about 5% of all cases.

These conclusions are corroborated by several retrospective analyses of safety studies on pharmaceutical drugs carried out in the context of the International Conference on Harmonization (ICH) for the registration of pharmaceuticals for human use. Over 90% of the drugs test elicited no toxic symptoms in one-year dog studies that were conducted in addition to prior 90- or 180-day dog or rodent studies. Another approach, in which the results from pre-clinical animal studies were compared with those from clinical studies, demonstrated that animal studies predicted about 70% of the effects observed in volunteers, and that in about 94% of the cases, these effects occurred in animal studies lasting no more than one month.

Based on these results, the report recommended abandoning the regulatory requirement for the routine carrying out of one-year dog studies. Also, while 90-day studies should be conducted in both dogs and rodents, chronic studies should only take place in rodents. In cases where dogs are more sensitive than rodents in the 90-day study, rather than conducting a one-year dog study, an additional safety factor should be applied to the NOAEL value obtained in the chronic rodent study in order to set an appropriate threshold for safe human exposure. This safety factor may be calculated from chronic NOAEL data available from several pesticide databases. Chronic tests using dogs would then only be required if the test compound belongs to a new class of chemicals that has never been tested before. Thus, the report concludes that, according to current scientific knowledge, routine one-year dog studies are no longer required for agricultural chemicals and pesticides, and international regulations should be changed

accordingly. Active international support of such measures is welcomed from both an economic and an animal-welfare perspective.

## Results of the Studies Conducted by the US EPA

The review performed by Baetcke et al. (2005) was based on a comprehensive database of registered compounds that is maintained by the US EPA. The authors showed for 77 compounds that data from dog studies had an impact on the derivation of reference doses.

The authors of the study concluded: *“Thus the present analysis indicates that a 13-week dog study would be adequate for identification of a NOAEL or LOAEL that would be similar to that established from a chronic dog study except 3 pesticides (3/77 or 4% of the cases evaluated.”* And *“Thus, the results of this current retrospective analysis of studies on pesticides, when considered with the results of the analysis by Spielmann and Gerbracht (2001), show, with few exceptions, that a 13-week dog study is as adequate as a 1-year dog study for identification of a NOAEL.”*

In 2006 the US EPA conducted additional analyses of dog studies conducted with pesticide chemicals (*Length of Dog Toxicity Study(ies) that is Appropriate for Chronic RfD Determinations of Pesticide Chemicals*). In this analysis a total of 110 pesticides representing more than 50 classes were scrutinized.

The authors of the study concluded: *“This larger analysis supports the conclusion that longer-duration studies (one year) in the dog do not result in appreciably lower NOAELs or identify new effects for the majority of chemicals when compared to the shorter-duration study 13-week study in this species. Thus, reliance on the required chronic rodent studies, two-generation rat reproductive study, and the thirteen-week dog toxicity study is generally expected to provide an adequate basis for chronic NOEL derivation in pesticide risk assessment. EPA acknowledges that there may be situations where a longer duration dog toxicity study may be warranted when a pesticide chemical is highly bio-accumulating (e.g. builds up in body fat) and is eliminated so slowly that it does not achieve steady state or sufficient tissue concentrations to elicit an effect during a 90-day study. EPA anticipates that this situation will be infrequent since current pesticides are not usually designed to be highly persistent and bio-accumulating. If such a chemical is encountered, EPA would require the appropriate tier 2 metabolism and pharmacokinetic studies to more precisely evaluate bioavailability, half-life, and steady state and determine if a longer duration dog toxicity study is needed.”*

Based on this conclusion, the US EPA removed the one-year study in dogs from the list of studies required for the regulation of pesticides.

## **Relevance of the One-Year Dog Study in Assessing Human Health Risks for Registration of Pesticides. An Update to Include Pesticides Registered in Japan**

A recent publication by Kobel et al. (2014) focused on Japan, which is considered a key region, and demonstrated the redundancy of the one-year dog study for agrochemical testing based on an analysis of data on the 400+ pesticides registered in that region. The setting of a so-called Acceptable Daily Intake (ADI), which defines limits on the amount of any particular chemical that a human should be exposed to over a lifetime, is a key means of protecting human health. ADIs derived from dog studies are available for 45 of these 400 pesticides, and these 45 ADIs were analyzed in detail. The study showed that excluding data from the one-year dog studies would have made no real difference in the setting of exposure limits for over 90% of these 45 pesticides. Additionally, there might have been a difference in 6.5% of the cases, and there would have been a genuine difference in the ADI recommendation in only 2.2% of the cases, which is to say, one chemical.

The retrospective data analysis showed that, in 99% of cases there would have been no significant impact on the safe exposure levels derived in Japan had the one-year dog studies not been conducted, and that in all cases consumer exposure would have remained well below the ADI.

This key publication adds substantially to the weight of published literature now indicating that one-year dog studies add no significant value to the safety assessment of agrochemicals. European regulations no longer require one-year dog studies. We now need to work towards a harmonized approach with countries in other parts of the world. The time has come for one-year dog studies to be removed from test requirements globally.

## **Discussion**

The limitations of each of these reviews are well understood as is the need for greater comprehensiveness, and Baetcke et al. (2005) have asked for a broader review of entire databases, not just the chemicals for which dog studies drive the safety assessment. In response to this, the US EPA performed an extensive review in 2006 and concluded that for pesticide risk assessment dog studies should be conducted for more than three months. There is no disputing the need for repeat-dose studies in dogs of three months' duration. The weight of evidence, however, of all these reviews together—and in particular the studies conducted in dogs (Gerbracht and Spielmann 1998; Spielmann and Gerbracht 2001; Box and Spielmann 2005; Doe et al. 2006; Baetcke et al. 2005; Kobel et al. 2010; US 2006)—shows conclusively that there is little value in conducting a one-year dog study in addition to a three-month study, which strongly suggests that such studies can be safely eliminated from the list of studies that are mandatory for the safety assessment of pesticides. Of all the chemicals in the databases analyzed in the four main publications critically reviewed here, only 3–4% had reference doses the setting of which was influenced by the results of a one-year dog study.

We consider the combined weight of evidence from these four reviews clearly demonstrates that dog studies for pesticides need be no more than three months long. The fact that each review arrived at a similar conclusion despite having taken a different approach to the subject matter provides additional support for our conclusion. In cases where dogs are apparently more sensitive than rodents in three-month studies a comparative evaluation for kinetics, and differences in dynamics should be analyzed.

Evidence from all of these reviews as well as from their combined consideration supports the conclusion that dog studies are necessary but can be limited to three months' duration without compromising human safety. Thus, as suggested in some of the reviews, improvements in study design are called for. Therefore, a balanced consideration from the scientific and animal welfare perspectives suggests that national requirements which are insisting on one-year dog studies for the regulation of pesticides should be updated in order to be in line with the regulations established in the EU and the USA, which would eliminate the requirements for dog studies longer than 3 months' duration.

## References

- Baetcke KP, Phang W, Dellarco V (2005) A comparison of the results of studies on pesticides from 12- or 24-month dog studies with shorter duration. US EPA, 4/7/05. <http://www.epa.gov/scipoly/sap/meetings/2005/may2/dogstudymay05.pdf>
- Box RJ, Spielmann H (2005) Use of dog the dog as non-rodent species in the safety testing schedule associated with the registration of crop and plant protection products (pesticides): present status. *Arch Toxicol* 79:615–626
- Doe JE, Boobis AR, Blaker A, Dellarco V, Doerr NG, Franklin C, Goddman JI, Kronenberg JM, Lewis R, McConnel EE, Mercier T, Moretto A, Nolan C, Padilla S, Phang W, Solecki R, Tilbury L, van Ravenzwaay B, Wolf DC (2006) A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. *Crit Rev Toxicol* 36:37–68
- EU Commission (2009a) Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on Cosmetic Products
- EU Commission (2009b) Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC
- Gerbracht U, Spielmann H (1998) The use of dogs as second species in regulatory testing of pesticides: I. Interspecies comparison. *Arch Toxicol* 72:319–329
- Health Canada Pest Management Regulatory Agency (HC PMRA) (2016) Guidance for developing datasets for conventional pest control product applications: data codes for parts 1, 2, 3, 4, 5, 6, 7 and 10. [http://www.hc-sc.gc.ca/cps-spc/pubs/pest/\\_pol-guide/data-guide-donnees/index-eng.php](http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/data-guide-donnees/index-eng.php)
- Kobel W, Feger I, Billington R, Lewis R, Bentley K, Bomann W, Botham P, Stahl B, van Ravenzwaay B, Spielmann H (2010) A 1-year toxicity study in dogs is no longer a scientifically justifiable core data requirement for the safety assessment of pesticides. *Crit Rev Toxicol* 40:1–15
- Kobel W, Fegert I, Billington R, Lewis E, Bentley K, Langrand-Lerche C, Botham P, Sato M, Debruyne E, Strupp C, van Ravenzwaay B (2014) Relevance of the 1-year dog study in assessing human health risks for registration of pesticides. An update to include pesticides registered in Japan. *Crit Rev Toxicol* 44:842–848

- Linke B, Mohr S, Ramsingh D, Bhuller Y (2017) A retrospective analysis of the added value of 1-year dog studies in pesticide human health risk assessments. *Crit Rev Toxicol* 47:587–597
- Russell WMS, Burch RL (1959) *The principles of humane experimental technique*. Methuen & Co. Ltd., London
- Spielmann H, Gerbracht U (2001) The use of dogs as second species in regulatory testing of pesticides. Part II. Subacute, subchronic and chronic studies in the dog. *Arch Toxicol* 75:1–21
- US EPA (2006) *Length of Dog Toxicity Study(ies) that is Appropriate for Chronic RfD Determinations of Pesticide Chemicals*. Washington, DC: Health Effects Division, Office of Pesticide Programs, US Environmental Protection Agency. March 20, 2006

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