Importance of Storage Stability Studies in the Development of Pesticide Formulations

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Manufacturers of pesticides must know the shelf life of their products for the most varied storage conditions. Accelerated storage tests at elevated temperatures can never completely substitute long-term tests under practical conditions. Nevertheless, a mathematical evaluation of analysis results can considerably raise the meaningfulness of such accelerated tests since predictions of the anticipated active ingredient decomposition under the many different temperature/time conditions are possible. An example is given to demonstrate that for this purpose only a small number of analytical data are needed. Without the degradation reaction order being determined, a sufficiently accurate estimate of the degradation rate can be made. This is demonstrated by a comparison of calculated and found levels of active ingredient content in a long-term storage test.

1. Shelf life guarantee of manufacturer

Manufacturers of pesticides usually have to give a certain shelf life guarantee for their products, which in many cases is for a period of two years. The guarantee states that at the end of this storage period, the product can still be applied without any trouble, that it will still produce its full biological activity against the pests which it is required to control, and that crop tolerance will not have been reduced.

Although this requirement sounds so simple, it poses large problems especially for those firms which export their pesticides to many countries where the products are then stored under greatly varying conditions.

In order to assess the storage stability of a product, consideration must be given to those factors capable of altering the properties of the product in the course of time. Rogers\(^1\) states that the factors responsible for degradation are light, temperature, acidity, alkalinity, oxidation and humidity. Another factor which most certainly must be taken into account in certain cases is externally applied pressure which may have a most decisive influence on the storage stability of powders packed in sacks.

2. Changes during storage

The most important changes occurring during storage are undoubtedly chemical changes of the active ingredient, in other words those usually described as degradation

\(^{*}\) Presented at the CIPAC symposium held in London on 7 June 1974.
of the active ingredient. In fact the greater part of this paper is concerned with this phenomenon. However, when it is considered that all formulations, with the exception of the true solutions, are thermodynamically unstable, it will be appreciated that various kinds of physical change can also occur.

A number of factors can be more or less completely eliminated by the use of a suitable package. For example, it is easy to protect a product against light during storage. Influence of atmospheric oxygen and humidity can similarly be eliminated by using appropriately tight packings. The use of drums instead of sacks minimises pressure load resulting from stacking.

3. Influence of temperature

There is, however, one very important factor which is capable of penetrating all packings, namely temperature. Its influence on the rate of chemical reactions is known, with Van't Hoff's law stating that a temperature rise of 10 °C increases the rate of reaction by two- to fourfold. It thus follows that, from the aspect of active ingredient degradation, the shelf life of pesticides is shorter in countries with warm climates than it is in the temperate zones.

Therefore, the countries of the world have been classified into three climatic zones (Table 1), based on the results of investigations into storage conditions in the various countries. When one of the given levels is exceeded in the climatic zones 1 and 2, the country concerned is classified in the next higher zonal category.

<table>
<thead>
<tr>
<th>Table 1. Classification in climatic zones</th>
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</thead>
<tbody>
<tr>
<td>Climatic zones</td>
</tr>
<tr>
<td>Average yearly temperature (°C)</td>
</tr>
<tr>
<td>Average summer temperature (°C)</td>
</tr>
<tr>
<td>Number of days with maximum temperature &gt;35 °C</td>
</tr>
</tbody>
</table>

On the basis of this classification, it is found that, for example, climatic zone 1 includes central and northern Europe, zone 2 includes Italy (excluding south Tyrol), southern France, Greece and Portugal, and zone 3 includes the tropical countries of America, Africa and Asia.

4. Changes of physical properties with temperature

It is, however, very difficult to estimate the influence of temperature on the physical properties of a pesticide. A few examples are discussed below.

Emulsifiable concentrates are usually true solutions and as already stated, are thermodynamically stable within a certain temperature range. Irreversible changes in their appearance or in their emulsion quality are, therefore, indicative of chemical alterations in the system. Consequently, these changes take place more quickly at high
temperatures than at low ones. On the other hand, low temperatures may have a far more harmful effect than high temperatures on emulsions and suspension concentrates. When the outer aqueous phase begins to freeze, the physical properties in the remaining liquid between the water crystals change so enormously that very often irreversible alterations occur. Such alterations may be intensified by frequent change of temperature.

Physical changes in dispersible powders chiefly occur at elevated temperatures. At a temperature level close to the melting point of the active ingredient, which under certain circumstances may undergo considerable eutectical depression due to the influence of the formulating aids, the active ingredient, carrier and dispersing agent frequently orient themselves in a completely different manner with the result that dispersibility may be greatly altered. Highly volatile active ingredients may undergo Ostwald ripening due to sublimation.

5. Accelerated storage tests

The formulation chemist often has only a very short period of time available in which to develop a new formulation. Therefore, he must conduct accelerated storage tests which enable him, after a relatively short time, to predict the shelf life of the product. What possibilities are there in a laboratory for accelerating storage, i.e. what possibilities are there for shortening the time? Firstly considering the active ingredient content; since the rate of chemical reaction is dependent upon temperature, a possibility is to store the product at elevated temperature. There are practical limits to the extent to which the temperature can be raised in order to shorten the duration of the test. Excessive deviations from practical conditions may result in a fundamental alteration of the mechanism and rate of degradation.

As standard tests, the following storage conditions have been found to be most suitable: 8, 16 and 24 weeks at 20 °C; 8, 16 and 24 weeks at 40 °C; 8 weeks at 50 or 54 °C. Two-week storage at 54 °C has recently also been adopted as an additional standard test as recommended in FAO specifications.

As a practical example, storage tests are now described conducted with “Volaton” (registered trade mark of Bayer, Leverkusen), an emulsifiable concentrate containing phoxim [α-(diethoxyphosphinooxyimino)phenylacetonitrile]. In this particular case, the product was stored under conditions far exceeding the standard ones mentioned above, i.e. up to 96 weeks at 20, 30 and 40 °C and 40 weeks at 50 °C (see Table 4). Consequently, it can be established to what extent the predictions that can be derived from the standard conditions are actually correct.

The product was stored in 100 ml glass and aluminium bottles. The data shown in Table 2 for the active ingredient content were found with aluminium bottles, but those for glass bottles were not significantly different.

On looking up the relevant literature for information regarding the mathematical analysis of such figures with the help of reaction kinetics and the Arrhenius equation, it is found that the order of reaction must first be determined. This, however, is not possible. A test referring to this with so few data and a relatively high standard deviation is bound to fail, as Figure 1 shows. The plot of the concentration c, its logarithm
and its reciprocal value vs time \( t \) does not indicate which of these functions is most likely to assume the shape of straight line. In practice it is at this point that many attempts at a mathematical analysis of accelerated storage test results fail.

Table 2. Phoxim content of "Volaton" e.c. after storage

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Storage time (weeks) 0</th>
<th>8</th>
<th>16</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>49.0</td>
<td></td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>49.0</td>
<td>48.4</td>
<td>46.4</td>
<td>46.2</td>
</tr>
<tr>
<td>50</td>
<td>49.0</td>
<td>45.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The standard deviation of the analytical method was found to be \( s = 0.60 \) percentage units.

Figure 1. Plot of functions of concentration against time for "Volaton" e.c. stored at 40°C.

On the other hand, it is possible to read the approximate gradients from the curves for zero, first and second order reactions. Figures 1 and 2 were evaluated, the latter showing the degradation data at 50 °C, and the rates of reaction listed in Table 3 were obtained. From the plot of the logarithm of the reaction rate constant \( k \) vs the reciprocal value of the absolute temperature, obtained by applying the Arrhenius equation, the reaction rate constants can also be read for other temperatures (Figure 3).
From the equations for the different orders of reaction, i.e.

- zero order: \( c = c_0 - kt \)
- first order: \( c = c_0 \exp(-kt) \)
- second order: \( c = \frac{1}{kt + 1/c_0} \)

the active ingredient content expected at the end of the whole test was calculated and compared with the values actually found (see Table 4).

It is evident from this table that the differences arising out of the different orders of reaction are very slight. This will be understood upon looking at Figure 4, a plot of the courses of reactions of different orders, which can be found in a similar form in many textbooks on physical chemistry.

The range which is of interest in connection with storage stability tests is between 0 and 20% degradation, in other words between \( c = 0.8 \) and \( c = 1 \). In this range, however,
the curves for the different reaction orders are very close together so that it seems unnecessary to make an exact determination of the reaction order in this range.

Returning to Table 4, it is obvious that the values found agree sufficiently well with those calculated. A more exact mathematical analysis, taking into account the data obtained during the course of the whole test, showed that the zero order rate holds best for the decomposition of phoxim. Figure 5 shows the degradation curves plotted at different temperatures. It also reveals that at that time, whilst phoxim was in the process of being developed, some difficulties were still being encountered with analytical method. At 32 and 64 weeks, all analytical values were too high, and at 48 weeks they were too low.

It is clearly evident from the graph that "Volaton", exposed to an average temperature of 30 °C, is storable for 2 years, if one accepts an active ingredient loss of 10%. Experience has shown that in most cases, an active ingredient loss of this order does not

<table>
<thead>
<tr>
<th>Storage temperature (°C)</th>
<th>Storage time (weeks)</th>
<th>Active ingredient content calculated (percentage units)</th>
<th>Active ingredient content found (percentage units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>96</td>
<td>Zero order 47.6</td>
<td>48.0</td>
</tr>
<tr>
<td>30</td>
<td>96</td>
<td>First order 47.6</td>
<td>45.2</td>
</tr>
<tr>
<td>40</td>
<td>96</td>
<td>Second order 47.4</td>
<td>33.7</td>
</tr>
<tr>
<td>50</td>
<td>40</td>
<td>Zero order 33.0</td>
<td>28.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First order 34.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second order 36.5</td>
<td></td>
</tr>
</tbody>
</table>
Storage stability of pesticide formulations

Figure 4. Rates of reactions of different order showing the same initial speed.

Figure 5. Decomposition rates of phoxim during storage of “Volaton” e.c. at different temperatures.

become manifest in the field. In some cases, still higher active ingredient losses can be accepted, without any significant reduction of biological activity.

It is extremely difficult for the formulation chemist to predict changes of physical properties occurring under actual storage conditions from an accelerated storage test. A mathematical analysis is not possible, and in fact it is not always known in which way changes that occur in practice can be accelerated at all without at once rendering
such a test unrealistic and incapable of being evaluated. Should the stability of an emulsion be tested by heating or cooling it, or by subjecting it to centrifugal stress or shearing stress? Only experience gained with similar products can provide the chemist with some indication of the procedure he should adopt for the tests required to be made, and a final answer can be given only by long-term storage tests under practical conditions.

6. Heat tests

A heat test is also contained in the FAO specifications and usually involves 14 days storage at 54 °C. In the light of that discussed above, such a test cannot be considered as constituting an accelerated storage test since it is not possible to extrapolate its results to other storage temperatures without knowing the relation of the reaction rate to temperature. However, by comparing it with a standard, it can be established whether the active ingredient stability of the tested product at elevated temperature is equal to, better or worse than that of the standard. In the FAO specifications, the standard is given by the degradation tolerances which are set for each individual product. To establish these tolerances, good knowledge of the products' characteristic features is essential.

At the same time, this test has the undisputed significance of constituting extreme storage conditions to which pesticides may be exposed for brief periods in the tropics.

For the production control check of a pesticide at the factory, such a two week test is usually much too long. Following appropriate experimentation, however, it can usually be substituted by a shorter test at higher temperatures but the results of this shorter test often hold only for a very particular formulation. For a formulation of the same type but using different formulating aids, the conditions may have to be very different. Therefore, the fact that shorter tests at higher temperatures were not included in the FAO specifications is welcomed. The risk of changes or reactions occurring in heat tests, which are not relevant to practical situations, becomes greater the more one departs from practical conditions.

References