PSAC . Tox Sub committee

PSAC TOX SUBCOMMITTEE MEETING

MINUTES OF THE MEETING HELD 29 MARCH 88

PRESENT :

Dr G M Farrell, Dev Dept
Dr L L Smith, CTL
Dr G A Willis, PSRSU
Dr N N Sabapathy, PSRSU
Mr N G E Geach, FEP
Mr I S Chart, RAS
Dr A Calderbank, C/O RAS
Dr T B Hart, Pharmaceuticals
Dr B P Domayne-Hayman, Herb Mgmt
Fua Jee Mok, Field Trials, J/H
Mr E Paterson, Herb Mgmt

1. RECOMMENDED SPRAY STRENGTH

NNS reported the results of the recent spray/absorption trial in Malaysia. The trial was conducted at a 1 in 40 dilution; 24 sprayers were involved; half in normal clothing and others allowing maximal exposure (eg T-shirts, shorts). Under the latter conditions an unexpected number of positive urine tests were found and spraying was halted at day 3. Medical examination revealed a significant number of skin lesions, 11/24 with nasal irritation and 5/24 with epistaxis. One member of the group was more severely affected. Recent analysis of results (only 12 available) has shown that all the maximally exposed sprayers had detectable levels of paraquat in plasma and one person from the other group (see attached). TBH observed that 1 in 40 was a maximum rather than a recommended concentration. The 0.5% was a compromise between the known effects of 1-2% spray dilutions and the 0.1% - 0.2% spray dilution information. When skin is intact there is very little absorption but the uptake is greatly increased if the skin is broken. The aspects of the trial were as close to normal working practises as possible.

LLS observed that

Weight 60 kg
Excrete 0.5 mg Pq total
Volume of distribution = 100 litres
Kidney only route of excretion then 500 µg in 100 litres give
5 µg/litre = 5 ng/ml

New methods of analysis allow for the detection of this sort of level of p Pq as opposed to the old method (~20 ng/ml)

LLS noted that the observed levels were too low to cause the lung lesion. AC asked if the actual formulation strength when a 'break' occurred. LLS mentioned the difficulty of using rat skin (approx 100 x faster) and human skin invitro does not show erythema and thus difficult to extrapolate. Direct experimentation in man has proved to be difficult for ethical reasons. TBH raised the point

of the effect of more prolonged exposure ie if the trial had been allowed to continue. LLS emphasised that there were no authenticated deaths with 2% or below spray dilution and that the dose response was very steep.

TBH mentioned the difference to the Sri Lanka study where the sprayers were maximally exposed but because of conditions they tended to wash frequently and thus appreciable absorption did not take place. The spray strength was 0.05% (1 in 400). TBH

The nose bleeds were thought to be due more to the type of spraying (epiphytic) rather than the concentration involved.

NNS noted that there was increasing pressure to use low volume spraying and the 1 in 40 statement on the label tends to imply that 1 in 40 (0.5%) is safe without specifying any special handling precautions. If the lowest dilution were changed there was general agreement that this should be 1 in 100 (0.2%). NG suggested that as the information was limited at the moment the region should be consulted for their view on dilution and then the problem reviewed. EP highlighted the commercial pressure of using low volume application and the 'political' impact of changing the recommended maximum dilution which would be interpreted as the compound being 'less safe' than before. GF and GMF was also concerned about recommending a change in dilution.

LLS raised the point of the detection of Pq in the plasma and the fact that this was the first time it had been observed and related this to the problem that may arise with the EPA.

LLS will arrange for the completion of the analysis ASAP NNS will discuss the practical details of spraying conditions with GC and GMF. GAW, NG and NNS will discuss with the regions the effect of implementation of a dilution change. LLS NNS/GC/GMF GAW/NG/NNS

2. RECOMMENDED EMETIC CONCENTRATION

LLS presented the view that as additional data were now available the subject of emetic concentration should be reviewed. Yoshioka and Volens had or would be publishing the new data soon.

The Preeglox formulation in Japan had the same concentration as before but as the Pq level was reduced the Pq/emetic ratio was reduced.

Survival rate was 40% for Preglox and 25% for Gramoxone. The time, after ingestion, to vomit was 12 min for Preglox and 40 min for Gramoxone. LLS observed that the mortality rate was disappointingly high with the Preglox ie there was very little change in mortality. The amount that people are taking when they attempt suicide is usually so much greater than needed that large changes are needed in emetic rate. LLS emphasised that the important point was the shortening of the vomitting time and its potential (hopefully) of saving lives.

BDH asked if there was any evidence that increased levels of emetic would actually decrease the vomitting time. LLS said that the information was only available in animals. LLS also pointed out that the increase in vomitting may make it difficult to treat with Fuller's Earth and there was also the problem of asphixiation on vomit.

Changes in the emetic concentration would lead to regulatory and cost problems particularly the former. NG highlighted the difficulty in going in again to Japan to alter the formulation. LLS is visiting Japan and the subject will be reviewed at the next meeting.

Multiple Emulsion Formulation

Diesel formulation gives solidification problems.

The Isopar formulation was suitable for spraying but with higher toxicity. A twin pack option was also being considered to allow for spray trials in August.

LLS noted that the major technical difficulties was the preparation of a suitable formulation and imaginative solutions may/would need to be found. The twin pack option is useful in that it keeps certain options open. Extra resource will be made available in the formulation section.

Status of Work on Stench/Blue dye

Current blue dye (Acid blue 1) is mutagenic and the option to change to Acid blue 9 (which is a food grade dye) is being explored. AB9 fades very slightly and would be used in WER. It would also assist in prevention of parallel imports.

ISC updated the meeting on the timing of the acute testing at CTL and the difficulty in carrying out the tests due to the animal attendants being affected. The results should be available mid-year. A sub acute inhalation study on VFT material will be conducted once the results of the acute screen are known (subject to budgetary constraint).

SDS formulation

The SDS formulation was originally rejected on the grounds of dustiness and lack of gelling properties. A new formulation is now available which is non-dusty and will form a gell at a 1 in 15 dilution.

GMF needs details of the current Preglox situation by the end of June ready for his visit to Japan. **LLS**