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Acute Dietary Risk Assessment – Workshop Report

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Project Number: AH01033

AH01033

This report is published by Horticulture Australia Ltd to pass on information concerning horticultural research and development undertaken for Australian Horticulture.

The research contained in this report was funded by Horticulture Australia Ltd with the financial support of all levy paying industries, AKC Consulting Pty Ltd and AVCARE.

ISBN 0 7341 0474 X

Published and distributed by:
Horticultural Australia Ltd
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Horticulture Australia

HAL Project Number: AH01033

Acute Dietary Risk Assessment - Workshop Report

Final Report

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Purpose of the Project:

To discuss progress in the development of methodologies used for acute dietary risk assessment, it's current status internationally, how it is planned to be implemented domestically and the potential implications for Australian agriculture.

AKC Consulting Pty Ltd acknowledges the funding support provided by the Horticultural Australia Limited for this project.

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TECHNICAL SUMMARY

A workshop on acute dietary risk assessment was held in Canberra, ACT, on April 11th 2002. The objectives of the workshop were to provide an update on progress in the development of methodologies used for acute dietary risk assessment, its current status internationally, how it is to be implemented domestically and the potential implications on current registered pesticide uses in agriculture. The workshop was seen as an opportunity for all involved to both share information and identify the key issues in the assessment process for further discussion.

The forty-five participants represented federal and state regulators, representatives of chemical manufacturers, representatives of various agricultural sectors, e.g., horticulture, grains, meat and dairy industries (refer to Appendix II for participants list). Six formal presentations were given to provide the participants with background on the methodology. The abstracts of these presentations can be found in Appendix I.

Issues of concern included a number of aspects of the methodology e.g., toxicology (estimation of the acute reference dose), consumption data (unit weights and portion sizes) and residues (variability factors), and the process to be followed should acute dietary exposure estimates indicate the possibility of an exceedance of the ARfD, i.e., how will such cases be managed in terms of new and or existing use pattens for agricultural chemicals in Australia.

An outcome of the meeting was an agreement to the following five resolutions.

Resolutions

1 That the issue of appropriate toxicological endpoints and associated safety factors in the determination of ARfD continue to be further refined. Such improvements will continue to reflect a more accurate understanding of the level and type of protection the public needs regarding the acute effects of pesticides contained in food. To this end it is recommended that this should be of continuing consideration by the ACPH.

2. Industries (agricultural and chemical) when responding to requests by the NRA for residue data for compounds where the ARfD have been calculated should include relevant edible portion data and more specifically, the residues associated with the edible portion.

3. Where possible ANZFA should expand the range of current surveys to generate data with respect to acute dietary exposure to pesticides.

4. That confidence limits be included in acute dietary exposure estimates produced by ANZFA's DIAMOND or other means.

5. That agencies prepare and share Information Fact Sheets related to acute dietary risk assessment with their stakeholders.

1 INTRODUCTION

BACKGROUND

Until recently the main focus for risk assessments relating to dietary exposure to pesticide residues has been chronic intake, i.e., long-term exposure to pesticides in the diet. The risk assessment focused comparing intakes with the Acceptable Daily Intake (ADI) of a given pesticide, which if ingested during an entire lifetime, would be without appreciable risk to the health of the consumer. During the last 10 years, significant improvements have been made by regulators nationally and internationally in the methodologies used for such purposes and Australian regulators are recognised for their significant contributions in this field.

More recently the focus has shifted to the issue of short-term dietary exposure, i.e. acute exposure. This area has increased in prominence due to the appreciation that some pesticides have measurable toxic effects due to their acute properties as well as the observed phenomenon of variability of residues in individual fruits and vegetables. That is, that residues on individual pieces of fruit or vegetables can vary significantly and that any single unit might have a residue higher than the maximum residue limit (MRL). For acute dietary intake estimates this is potentially significant as MRLs are set on the basis of residues found in composite samples from residue trials. This has led to the development of the concept of assessing the risk of exposure to the consumer of the eating a large meal size portion of fruit or vegetable containing a residue near to the highest concentration likely to occur as a result of good agricultural practice.

The subject has been raised, discussed and progressed at various international fora, e.g., the 1997 Geneva Consultation,[1] followed by the International Conference in York[2], the *ad hoc* Expert Meeting held before the 1999 session of the CCPR[3] and further refined at the 1999 JMPR[4] meeting. The concept is now incorporated into chemical reviews being undertaken internationally by JMPR and various national governments, e.g., USA, Canada and various EU member countries. However, currently there is no universally accepted methodology to evaluate acute dietary risk exposure with different countries taking differing approaches. Currently two methodologies exist: the conventional or deterministic model, where single point estimates are calculated and the probabilistic model, which attempts to model the distribution of exposures in a population. In risk assessment, the deterministic approach compares estimated exposure to a toxicological benchmark called the acute reference dose (ARfD), whereas the probabilistic approach compares the theoretical exposure distribution to a distribution which is considered to present an acceptable risk to consumers (in the US less than 0.1% of the population exposed to greater than the ARfD).

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[1] WHO 1997b "*Food Consumption and Exposure Assessment of Chemicals*" – report of the FAO/WHO Consultation, Geneva, Switzerland, 1997.

[2] PSD 1998 *Pesticide Residues Variability and Acute Dietary Risk Assessment* York, UK, December 1998.

[3] Joint FAO/WHO Meeting on Pesticide Residues. 1999

[4] Codex Committee on Pesticide Residues. 1999.

In Australia the incorporation of acute dietary risk assessment began in 2000[3]. The initial approach has been to use the deterministic methodology. However, ANZFA is considering the probabilistic approach but only from a feasibility perspective at this stage. The current approach is based upon an NRA/ANZFA memorandum of understanding for dietary exposure evaluations. The responsibility for calculation of ARfDs rests with the Therapeutic Goods Administration (TGA). These are then provided to the NRA which then calculates estimates of short term dietary exposure and undertake the risk assessment. The outcome of the risk assessment is passed to ANZFA.

For the sake of clarity, the ARfD is calculated by the following equation:

ARfD = Appropriate toxicological end point incorporating a factor to allow for possible differences in inter- and intra-species sensitivities.

The amount of pesticide residues ingested is calculated similarly:

Estimate of acute intake = Residue in commodity (including any variability factor) multiplied by the large portion size consumed divided by the body weight

The complexity of the issue of acute dietary risk therefore is derived from all of the above factors that lead to assessment of the acute dietary risk. If the estimate of acute intake is greater than the ARfD, then it cannot be concluded using the deterministic model that there is no acute dietary risk to the consumer.

A potential outcome of this process is that if the ARfD is exceeded by an estimate of acute exposure, MRLs will either not be promulgated for new chemicals or will be removed for existing chemicals, potentially stopping or removing pesticide uses. Outlined below is a summary of discussions undertaken at the workshop covering aspects of the methodologies and processes being employed by Australian regulators.

2 SUMMARY OF GROUP DISCUSSIONS

The Chairman highlighted the primary factors that lead through the risk assessment, risk management and risk communication process. It was noted that three separate scientific components are essential and that all three come together collectively in order for regulators to reach the stage of making decisions on the continuance of existing, or establishment of new, use patterns in Australia. These components, establishment of the acute reference dose (ARfD), the estimate of the amount of the commodity consumed and the relevant pesticide residue level in that commodity, are addressed below.

2.1 METHODOLOGICAL CONCERNS

2.1.1 Residue data

[3] See abstract by S Crossley in this report.

In the deterministic approach the pesticide residue data used in estimating exposure are derived from specific residue field trials conducted under conditions likely to produce the highest residues consistent with good agricultural practice (GAP). However, there is no recognition that the residue values from such trials may not necessarily reflect existing farming practices whereby application rates and frequency of applications may be less than the allowed maximums and preharvest intervals may be longer than the legally permissible minimums. These circumstances can arise from implementation of IPM strategies and/or low pest pressures. The primary assumption in using such data from specific residue field trials is that these data MAY reflect some current legal use pattern and the deterministic model is required to take this into account in the absence of more contemporary use pattern data.

2.1.2 Residue variability

For many foods eaten as individual units, or part thereof, e.g., apples, potatoes, lettuce or a bunch of grapes, composite residue data do not reflect the residue in a meal-sized portion. In such cases the deterministic approach employs a variability factor to allow for the possible unit-to-unit variability in residue concentrations. In the absence of actual data to indicate the true variability, conservative default factors of 5, 7 or 10 are used depending upon the commodity concerned. The factor is applied to the highest residue detected in composite samples from supervised field residue trials in order to estimate a high level of exposure. The meeting was informed that more information was needed on residue variability to enable more reliable estimates of exposure.

Data indicating the extent of residue variability for some pesticide/commodity combinations exists internationally but little is available from Australia. It was suggested that consideration should be given to generating variability data locally. Having unit variability data would remove the need for employing default variability factors. However, it was questioned whether the Australian situation would differ markedly from that of overseas.

It was further suggested that consideration be given to identify the sources of the variability. This would provide an opportunity for targeted research to either remove or reduce that variability, which could be of potential value through risk mitigation (e.g. certain methods of application of pesticides).

2.1.3 Residue definitions

The issue of the appropriate residue definition was raised, i.e., that in the risk characterisation undertaken by TGA only toxicologically relevant residues should be used and not necessarily just a convenient definition that permits easy enforcement of good agricultural practice. It was indicated that at JMPR two residue definitions can be used, one for monitoring and regulation purposes and a separate definition for dietary risk assessment. It was indicated that this issue required clarification.

2.2 DIETARY CONCERNS

2.2.1 Dietary data

The lack of unit weight data was identified as an issue of concern, particularly where the unit edible weight of the raw commodity is less than the large portion weight. It was identified that for many commodities there was either insufficient data or the data was inconsistent and that there was no standardized method for determining unit weights.

A significant component of the assessment process is the portion size data used. Currently, a 97.5th percentile consumption level (eaters only) is used. However this data applies only to those that consume the large portion (actually 2.5 % of those people who ate the commodity during the period when the consumption data was collected). Australian consumption data are contained in the ANZFA DIAMOND database. This database consists of data compiled in 1995 from 13,800 people. It was indicated that in order to determine the 97.5th percentile high consumption weight at least 41 respondents were needed, i.e., approximately 0.3% of the people sampled must have consumed the commodity during the survey period.

It was suggested that it would aid transparency if confidence limits could be added to the output of the DIAMOND database. This would provide a clearer picture of the actual meal-size portion that is an integral component in undertaking the risk assessment for acute dietary exposure.

The question of the completeness of food descriptors used in the Australian survey was raised. Apparently, at JMPR consumption data can sometimes refer to all uses of a commodity, e.g., apple data will include juice, processed apple as well as the raw commodity. It was indicated that the food descriptors used in the Australian survey were detailed enough to delineate raw commodities.

2.2.2 Future Surveys

It was generally agreed that it would be of value to improve the information held in the DIAMOND database. It was indicated that DHAC and ANZFA were currently considering another survey, which would probably occur within the next few years. It was requested that an opportunity be given to risk assessors to have input into the structure of the survey so that data of specific concern for acute risk assessment could be collected. It was also acknowledged that some trade-offs may be needed as the cost of generating large data sets could be prohibitive.

2.3 TOXICOLOGY

2.3.1 Evidence of harm

Queries were raised from the floor regarding what evidence existed of actual harm from acute dietary exposure to pesticides? It was acknowledged that no such evidence existed

where good agricultural practices were followed, i.e. in the instances where frank illness did occur from acute dietary exposure, this was due to illegal use of pesticides. However, it was pointed out that the methodology is not looking at effects but at exposure, i.e., attempting to identify theoretical acute exposure levels. It was suggested that the prudent conservative approach taken when establishing ARfDs should shield consumers from potential adverse acute effects. It was also suggested that acute effects may be prevalent, e.g., gastro-intestinal disturbances which cannot be definitively linked to exposure to pesticide residues.

Nevertheless, concerns were raised that unless placed in an appropriate context the application of the transitional methodology for assessing acute dietary exposure could lead to inverted health priorities; specifically, resulting in the devaluing of the health benefits of eating fresh fruit and vegetables.

2.3.2 Derivation of ARfD

It was acknowledged that the current approach in determining an ARfD is conservative. The value is calculated on the basis of toxicological studies allowing the identification of toxicologically significant end-points followed by the incorporation of 'safety' factors, e.g., 10 fold reduction for variation in human response to pesticides as well as another 10-fold reduction for intra-species differences (i.e. extrapolating from effects seen on animals to those that might occur in humans). As the concept is relatively new, for many compounds (either those undergoing formal review by the NRA or for new chemical entities) appropriate short-term studies do not exist. Consequently sometimes existing studies (or subsets thereof) designed to measure chronic effects are used. The applicability of this approach was questioned, i.e., whether it was appropriate to establish an ARfD if appropriate data were not available?

Currently there is not an internationally agreed protocol for the conduct of studies to allow the setting of an ARfD. It was indicated that a protocol being used in the US would probably be the basis for the international protocol once developed. This is a critical issue as it was indicated, by representatives of the chemical manufacturers, that if such data was not available from international sources it was unlikely to be funded locally.

2.3.3 Toxicological end-point

The concept of harm was raised in the context of what acute dietary exposure risk assessment process is attempting to address. While the JMPR has stated that pesticide use can occur in the absence of "appreciable health risk to the consumer on the basis of all known facts at the time of evaluation", there seems to be no consensus on what actually constitutes "appreciable health risk". The meeting did not specifically clarify this issue. The elaboration of the level of harm that this new methodology is attempting to address is key to identifying what toxicological endpoints are relevant. Whether the risk assessment process uses a NOEL (no observable effect level), NOAEL (no observable adverse effects level) or even a LOAEL (low observable adverse effects level) is predicated on defining the harm that the public is to be protected from. Furthermore the issue of relevant safety factors that are then applied to toxicological endpoints can also be

considered in the light of the concept of harm. The severity, reversibility and relevance of clinical effects were considered issues worthy of careful consideration.

Consequently, end-point selection is crucial in setting ARfD. If the end-point used is too conservative, the resulting ARfD could result in an over estimate of risk. TGA informed the meeting that they aim to keep flexibility in the system to allow ARfD and the methodology for their establishment to be refined if new data becomes available. It was suggested that this should be an issue addressed and refined with the assistance of the ACPH.

2.4 Risk management

Given that the methodology is still under development the question was raised that perhaps regulators should be waiting until the methodology is more refined before using it to make regulatory decisions which may be precipitous. Concerns were also raised that the methodology was being implemented with little or no input from AFFA and DHAC and that such implementation was already having effects on both the promulgation of MRLs as well as NRA approval of uses.

2.4.1 Chemical reviews

The question was asked concerning the approach to be taken if estimated short-term exposure level were identified as problematic. The NRA position was that the acute dietary risk assessment was seen as a screening tool. In the first instance the consumption data, the residue data and the toxicological data, used in the risk assessment, would be critically reviewed with regard to adequacy and to identify potential areas in need of refinement or data deficiencies. Should commitments to generate data be forthcoming an interim period could be given to allow this to happen during which time use of the pesticide in question would occur. However, the size of the estimated risk would determine the length of time provided and such issues would necessarily be dealt with on a case-by-case basis.

It was indicated that if the assessment was part of an existing chemical review ANZFA would not seek to remove an existing MRL if risk mitigation or data generation was underway to enable the refinement of the risk assessment.

However for new actives, uses, or permits, such periods of grace are unlikely to be available. If the best-estimated acute exposure is problematic, it is doubtful that a new use pattern could be approved.

2.5 Risk communication

It was suggested that the risk assessors in the NRA and ANZFA need to ensure that all stakeholders are kept fully informed of acute dietary risk assessment procedures, as they are currently applied and as the methodology develops.

3 RESOLUTIONS

1. That the issue of appropriate toxicological endpoints and associated safety factors in the determination of ARfD continue to be further refined. Such improvements will continue to reflect a more accurate understanding of the level and type of protection the public needs regarding the acute effects of pesticides contained in food. To this end it is recommended that this should be of continuing consideration by the ACPH.

2. Industries (agricultural and chemical) when responding to requests by the NRA for residue data for compounds where the ARfD have been calculated should include relevant edible portion data and more specifically, the residues associated with the edible portion.

3. Where possible ANZFA should expand the range of current surveys to generate data with respect to acute dietary exposure to pesticides.

4. That confidence limits be included in acute dietary exposure estimates produced by ANZFA's DIAMOND or other means.

5. That agencies prepare and share Information Fact Sheets related to acute dietary risk assessment with their stakeholders.

Acknowledgements

The authors of this report gratefully acknowledge the contributions made by attendees and those preparing presentations for the workshop. This workshop was also supported in part by contributions from Avcare, GRDC, the NRA and ANZFA.

APPENDIX I - *Acute Dietary Risk Assessment Workshop Presentation Abstracts*

Author	Paper
S Crossley – ANZFA	Acute Dietary Risk Assessment – History & and ANZFA perspective
L Davies – TGA	Determination of Acute Reference Dose
G Thomas - NRA	Acute Dietary Risk Assessment – Its application by the NRA
D Hamilton - QDPI	Acute Dietary Risk Assessment at JMPR
P Bowles - QDPI	Unit variability
R Tomerlin – Novigen Sciences	Probabilistic Risk Assessment in the USA

ACUTE DIETARY EXPOSURE - HISTORICAL PERSPECTIVES AND ANZFA POSITION

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Introduction

Since the 1980s, Australia has applied international scientific methodology in the assessment of risk arising from pesticide residues in food. Traditionally, Australian and international regulatory attention focussed exclusively on the risk arising from long-term (chronic) dietary intake. However, in the mid-1990s, the Codex Committee on Pesticide Residues (CCPR) recognised that risk arising from short-term (acute) dietary intake is important & needs to be addressed separately.

History of the development of acute dietary risk assessment methodology

The basic methodology for assessing acute dietary risk was developed at two international joint Food and Agricultural Organisation and World Health Organisation (FAO/WHO) Consultations. These Consultations aimed not only to elaborate methodology that could be used at the international level by the JMPR and CCPR but also to provide recommendations to national governments.

The first Consultation held in York, United Kingdom (UK) on the *"Revision of the Guidelines for Predicting Dietary Intake of Pesticide Residues"* in May 1995 provided updated guidance for estimating dietary intake of pesticide residues. This Consultation focussed primarily on chronic dietary intake and no detailed methodology for the estimation of acute dietary intake was developed. However, the Consultation agreed that an assessment of acute dietary risk should be routinely considered at the international level.

The second Consultation was held in Geneva in February 1997 on *"Food Consumption and Risk Assessment of Chemicals"* (hereafter named the "Geneva Consultation"). In developing intake methodology, this Consultation named the estimates of acute dietary intake the *International* or the *National Estimate of Short-Term Intake* (IESTI or NESTI).

The dietary intake methodology developed in Geneva has since been further elaborated by the Joint FAO/WHO Meeting on Pesticides (JMPR) and by break-out groups at an international conference on *"Pesticide Residues Variability and Acute Dietary Risk Assessment"*, hosted by the UK government in December 1998.

Why is acute dietary risk assessment important?

In considering the issue of the dietary risk assessment, the international Consultations and the JMPR recognised that the traditional dietary risk assessment methodology did not

adequately address the issue of acute dietary risk for a number of reasons. Firstly, many pesticides have toxicological end-points that are realised after short-term exposure, not the lifetime exposure that is assumed in the establishment of the Acceptable Daily Intake (ADI). Secondly, while it was realised that transient exceedances of the ADI are not of concern when considering chronic effects, this is not the case for acute effects on which some ADIs have historically been based. Thirdly, new data on the variability of residues within the composite samples on which maximum residue limits (MRLs) are based, highlighted the fact that residue concentrations in individual commodity units (eg. a single apple) might significantly exceed the MRL. Finally, it was agreed that the food consumption data used when estimating chronic dietary intake was not appropriate for the estimation of acute dietary intake.

Deterministic intake versus probabilistic intake methodology

The Geneva Consultation agreed that probabilistic intake methodology was potentially the best approach since it allows consideration to be made of more than one commodity at a time and estimates the probability that a given level of dietary intake could be reached. However, the Consultation recognised that to gain the full potential of probabilistic modelling detailed consumption and residues data are required and the technique is very time consuming to undertake. The Consultation therefore recommended alternative deterministic approaches that could more readily be applied. Two different methods were developed; the method applied depends on whether it is necessary to take account of the variability of residues between individual commodity units.

The first method is for food commodities where *the available composite residues data reflect the residues levels in the commodity as consumed.* Cherries is an example where several individual commodity units are normally consumed on each eating event and sample compositing therefore takes place at the time of consumption. The second "case" is for those food commodities where *the available composite residues data do not reflect the residue levels in the commodity as consumed.* Apples are an example where only one or a small number of individual units are usually eaten in a single sitting or meal and the possibility of a consumer eating a high variable residue needs to be taken into account. The calculation of dietary intake under the second method takes into account the potential for high residue variability by the incorporation of a variability factor v, where v reflects the potential ratio of a high level residue in the individual community unit to that found in a composite sample. A third method was later added to take into account the consumption of a portion of large items, such as melons.

Implementation at the international level and within Australia

At the international level, the JMPR have been establishing acute reference doses (acute RfDs), similar to a short-term ADI, since 1995. Furthermore, acute dietary intake estimates have been conducted by the JMPR since their 1999 meeting. In considering the advice of the JMPR, the CCPR has agreed not to advance recommended MRLs for adoption by the Codex Alimentarius Commission while the best estimate of acute dietary intake exceeds the acute RfD.

National governments, notably the USA, Canada and the UK, implemented comprehensive national acute dietary risk assessment policies in the mid-1990s which have been applied routinely for all regulatory decisions. Over the last few years the European Commission has been taking an increasing active role in this area and in the late 1990s, acute dietary risk assessments were incorporated as an integral part of all European Union pesticide evaluations.

In Australia, ANZFA and the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) have been undertaking acute dietary risk assessments using the deterministic methodology since 2000 for all pesticides for which there is an Australian or JMPR acute RfD. The NRA does not approve pesticide products, and MRLs are not recommended by ANZFA for incorporation into the Food Standards Code (FSC), until the acute dietary risk has been demonstrated to be acceptable.

ANZFA position on acute dietary risk assessments

ANZFA has the role of considering applications for Australian MRLs and recommending these to the Australian jurisdictions for incorporation in the FSC. The final decision on all these recommendations is made by the jurisdictions at the Food Regulation Ministerial Council.

In considering MRLs applications, ANZFA has to adhere to its statutory objectives. In particular, ANZFA cannot recommend an MRL to the Ministerial Council unless it can be sure that public health and safety are not compromised. In practise this means that the best estimate of acute dietary intake must not exceed the acute RfD, where one is available. This is the case even when it may be recognised that either the acute RfD or the estimate of acute dietary intake is conservative due to lack of data or limitations in the methodology applied. In undertaking its role, ANZFA has to also take account of agreed international standards or guidelines and ensure that there is adequate public consultation.

ANZFA is currently investigating the feasibility of establishing a probabilistic dietary intake methodology capability. However, probabilistic modelling is very resource intensive and will identify dietary intake scenarios that exceed the estimate arising from use of the deterministic methodology. Probabilistic methodology should not therefore be considered as a panacea by the agrochemical and agricultural industry in its desire to retain pesticides with significant acute toxicology.

Conclusions

Over the last few years, considerable international attention has been directed towards considering the acute risk arising from the dietary intake of pesticide residues, with a detailed deterministic methodology being developed at the international level. This attention has resulted from the realisation that the traditional chronic dietary intake methodology did not adequately address the risk arising from short-term dietary intake. The ANZFA and NRA have been applying the international methodology for the determination of dietary intake since 2000.

Useful background references

ACP (1997) *Unit to unit variation of pesticide residues in fruit and vegetables.* UK's Advisory Committee on Pesticides. Available from Pesticide Safety Directorate, York. February 1997

CAC (1996a). *Request for comments on revised Guidelines for the prediction of the dietary intake of pesticide residues*, Paper for the 29th session of the CCPR, Nov 1996, CL 1996/33 - PR

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SHORT-TERM DIETARY INTAKE ASSESSMENTS – ESTABLISHMENT OF ACUTE REFERENCE DOSES

Dr Les Davies, Chemicals and Non-Prescription Medicines Branch, TGA, Department of Health and Ageing

The Chemicals Unit, located within the Therapeutic Goods Administration of the Department of Health and Ageing (DoHA) provides toxicology and public health advice on agricultural and veterinary chemicals to the National Registration Authority for Agricultural and Veterinary Chemicals (NRA). This includes provision of advice on applications for approval of technical-grade active constituents (TGACs) and registration of agvet products, the establishment of first aid and safety directions for product labels, and the establishment of
Acceptable Daily Intakes (ADIs) for use in establishing the safety of long-term intakes of low levels of pesticide residues in food. Over the past several years, the Chemicals Unit has also used the toxicology data to establish a so-called Acute Reference dose (ARfD, or acute RfD).

The Acute Reference Dose has been defined by the WHO as an "estimate of the amount of a substance in food or drinking-water, expressed on a body-weight basis, that can be ingested, usually during one meal or one day, without appreciable health risk to the consumer". The ARfD provides the reference point in the acute dietary risk assessment.

The ADI, a health standard utilised for chronic intakes of dietary pesticide residues and food additives, was proposed in the early 1950s and was based on the threshold hypothesis for the toxic effects of chemicals. The ADI concept implies a "reasonable certainty of no harm", but there is a general recognition that ADIs can be exceeded for "short periods of time" without significant health effects.

The **acute** effects of chemicals have been recognised in the occupational setting for many years (eg. Short-Term Exposure Limits, or STELs) but the genesis of concept with respect to pesticide residues is less clear cut. In 1990 the International Programme on Chemical Safety (IPCS) stated[4] that "consideration should be given to the potentially acute toxic effects that are not normally considered in the assessment of the ADI". This was partly in response to various acute poisoning incidents with pesticides (eg. aldicarb on melons and cucumbers). In 1994 the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) considered issues relating to acute dietary risk and agreed that "short-term ADIs" for single exposures would be called acute reference doses. In the following year the JMPR established its first set of ARfD values and discussed ARfD-setting procedures, especially with respect to cholinesterase inhibiting pesticides. In the latter part of the 1990s, acute dietary intake estimates of pesticide residues became an important element of JMPR/CCPR[5] risk assessment process and considerable progress has been made in developing and refining the methods used to estimate intakes.

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[4] IPCS (1990) Principles for the Toxicological Assessment of Pesticide Residues in Food. WHO/FAO/UNEP International Programme on Chemical Safety (IPCS). Environmental Health Criteria No.104, page 81

[5] CCPR – Codex Committee on Pesticide Residues

In February 2000 the TGA advised the NRA that ANZFA was planning to undertake short-term dietary intake assessments on a routine basis and thus, that the TGA would proceed to set ARfDs; the NRA agreed that it was "appropriate for Australia to undertake acute dietary exposure on a routine basis for all Chemical Review Program (CRP) chemicals and new active constituents". The TGA has established a detailed database which contains (as at March 2002) ARfD values for approximately 80 agvet chemicals. However, at both the national and international level, there is ongoing consideration of important issues underlying the Acute Reference Dose concept and the appropriate toxicological end-points on which to set them.

ACUTE DIETARY RISK ASSESSMENT FOR THE REGISTRATION AND REVIEW OF AGRICULTURAL AND VETERINARY CHEMICALS IN AUSTRALIA

George Thomas, Senior Evaluator, Chemistry and Residue Evaluation Section, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240 Kingston, ACT 2604 Australia.

As part of the evaluation process for a new chemical or the reconsideration of an existing chemical the National Registration Authority (NRA) must be satisfied that the use of the chemical would not pose an unacceptable risk to people exposed to its residues in food.

There are two primary steps in the evaluation of potential residues in food:

- A toxicological evaluation conducted by officers of the Chemicals Unit, located within the Therapeutic Goods Administration of the Department of Health and Ageing (TGA) who provide their recommendations to the NRA. The evaluation includes the recommendation of an Acceptable Daily Intake (ADI) and an Acute Reference Dose (ARfD).
- A residue and dietary exposure evaluation is conducted by officers from the Chemistry and Residues Evaluation Section at the NRA. The evaluation includes the recommendation of appropriate maximum residue limits (MRLs) and withholding periods that are consistent with good agricultural practice. The estimated dietary exposures are compared to the ADI and/or ARfD determined in the toxicological evaluation. A risk assessment is made as to whether the proposed or continued use of the chemical would pose an unacceptable risk to human health.

  Where the toxicological and residue evaluations indicate that the risk to human health from dietary exposure is below the ADI / ARfD the MRLs are incorporated into the NRA's *MRL Standard.* The MRLs are also conveyed to the Australia New Zealand Food Authority (ANZFA) for incorporation into the *Food Standards Code.* Both NRA and ANZFA have public consultation obligations prior to incorporating new MRLs into their respective Standard or Code.

  Chronic dietary exposure has been considered in the Australian registration process for many years and the principles for estimating chronic exposures are relatively well developed and internationally accepted.

  The NRA is also obliged to consider the human health aspects of acute dietary exposure when an ARfD has been established for the chemical in question. The TGA has established ARfDs for some new active constituents and chemicals being considered in the NRA's Chemical Review Program.

  Methods for estimating acute dietary exposure to chemicals are continuing to evolve internationally with the two approaches being the deterministic and the probabilistic methods. The NRA's approach has been to use the deterministic estimates developed

by the Geneva Consultation[6] and most recently refined by the Joint Meeting on Pesticide Residues[7]. The NRA and ANZFA collaborate in the exposure assessment to make best use of available residue and food consumption data. Evaluators use the deterministic method to identify possible exceedences of the ARfD and then look critically at the available toxicology, residue and food consumption data to determine the significance of the result.

Where the NRA's most refined estimates of acute dietary exposure indicate a possible exceedance of the ARfD, data gaps will be identified and there may be negotiation with interested parties to provide data to support a revised risk assessment. Examples of data that are likely to be useful in revising initial acute dietary estimates are:

- New studies showing residues in edible portions and/or processed fractions
- Determination of residues in single units of some fruits
- New toxicological studies specifically designed to identify short term exposure effects

Where there is no scope to further refine the acute dietary estimate and the NRA cannot be satisfied that the risk to human health is acceptably low then risk management options would be considered. Initial options may include modification of the use pattern to reduce dietary exposure.

The NRA, in consultation with ANZFA and TGA, will continue to monitor developments in the science of acute dietary risk assessment. The key objective is to make the best use of available data to make scientifically based risk assessment decisions that are realistic, justifiable and adequately protective of public health.

[6] FAO/WHO (1998). Report of the Joint FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals, February 1997, Geneva, Switzerland

[7] FAO/WHO (2000) Pesticide Residues in Food-2000, Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

CURRENT JMPR PRACTICES IN ESTIMATING SHORT TERM DIETARY INTAKE OF PESTICIDE RESIDUES

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The focus of dietary risk assessment for pesticide residues has, until recently, been on the hazards arising from chronic intake, but now we must answer questions about the effects of short-term residue intakes that may be higher, on a daily basis, than the chronic intake.

JMPR has assigned acute RfDs (acute reference doses) to 34 compounds (33 pesticides and metabolite propylene thiourea). On the basis of the toxicology JMPR has decided for some compounds that a short term dietary intake of residues was unlikely to present a risk to consumers and it was unnecessary to establish acute RfDs (23 pesticides and metabolite *N*-acetyl glufosinate) or to estimate IESTIs (IESTI: International Estimated Short Term Intake).

The JMPR currently uses four different calculations for acute intake, depending on the situation:

- Case 1: residue in a composite sample reflects the residue in a meal sized portion.
- Case 2a: composite residue data do not reflect residue levels in a meal sized portion and the portion consists of more than one up to several units of fruits or vegetables.
- Case 2b: composite residue data do not reflect residue levels in a meal sized portion and the unit weight equals or exceeds the large portion size.
- Case 3: processed commodity where the likely highest residue is the STMR-P (supervised trials median residue for a processed commodity) because of bulking and blending, e.g. flour, vegetable oils and fruit juices.

The large portion size was chosen as the 97.5^{th} percentile consumption per day for eaters of that food. For JMPR evaluation purposes the highest national 97.5^{th} percentile consumption was chosen for each commodity. The food commodity unit weight in Case 2 calculations has a strong influence on the calculated intake. The unit weight is chosen from the region where the trials and registered uses support the Codex MRL.

The variability factor was devised to deal with the situation where the residue in the composite sample, say 5-10 fruits making up the 1-2 kg composite sample, could be imagined to arise from only one of the units of fruit. Then the residue in the single unit would be, on this conservative assumption, at a level 5-10 times as great as that in the composite. A generic variability factor of 4 would be suitable in most cases, but conservative values of 5, 7 and 10 are used in defined situations.

The data for JMPR intake estimations are essentially available from the supervised residue trials already provided for MRL estimation.

If the JMPR estimates of short-term intake for a compound exceed the acute RfD for one or more food commodities after all the available information has been taken into account, a footnote will be attached to those commodities in the MRL recommendations table:

> *"The information provided to the JMPR precludes an estimate that the dietary intake would be below the acute RfD."*

UNIT WEIGHTS OF INDIVIDUAL FRUIT AND VEGETABLE COMMODITIES

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There is now international awareness that short-term intakes of pesticide residues may be much higher on a daily basis than chronic intake. The variations in pesticide residue levels occurring in individual units of fruit and vegetables within a single lot can be such that a single unit might have a higher residue than the composite. For the calculation of acute dietary intake in the case where the unit edible weight of the raw commodity is less than the large portion weight, the formula for the International Estimate of Short Term Intake (IESTI) expressed as mg/kg bw/day is IESTI = [U x HR x v + (LP-U) x HR] / bw, where U is the unit weight (edible portion) provided by the country in the region where the trials gave the highest residue supporting the MRL.

In late 1999, in the absence of clearly defined overseas methods for determining unit weights, we chose to make contact progressively with a variety of people working in the fruit and vegetable industries to ascertain what Australian unit weight data were readily available, with the retail sector being regarded as the most realistic potential source of the information. Data were sought on unit weights (full weight and edible portion weight) of the most common size of each commodity sold in the marketplace. Published data, notably Cashel et al, Composition of Foods, Australia, 1989, and research publications by Professor Ron Wills, University of New South Wales, were also accessed.

Overall, respondents indicated that actual data on typical unit weights had never been sought. Growers and specialists connected with individual industries drew attention to the marked size variation within individual commodities, including sizes commonly marketed in different parts of Australia. The Quality Assurance Unit of the Fresh Produce Section of Franklins Limited, however, provided a considerable amount of data, utilising their bar code systems to establish the most common sizes of commodities sold. The Australian and New Zealand Food Authority (ANZFA) also provided data from the Technical File of the Australian Food and Nutrient Database 1999 (AUSNUT). All data, together with specialist opinions, were incorporated into a spreadsheet. The median values were then determined for each commodity where possible, as explained by worked examples.

Figures derived from the United States Department of Agriculture Nutrient Database for Standard Reference in general tended to be well below typical unit weights in Australia, particularly in relation to tropical fruits and vegetables. The Explanatory Notes attached to the Technical File of AUSNUT indicated that the vast majority of the data were derived from the US Codebook files and adjusted to metric measures.

The Technical File contained no unit weight data for 34 separate fruit or vegetable commodities for which data were gathered in this small-scale project. There were also thirteen cases (tropical fruit, citrus and vegetables) where unit weight data from other sources were not able to be easily reconciled with the unit weights listed in the AUSNUT technical file. Further work on gathering Australian data on fruit and vegetable unit weights would be desirable under the auspices of a nationally focussed project. There is clearly a need for agreement at government level on the best approaches to follow for establishing typical unit weight data relevant to individual countries.

PROBABILISTIC RISK ASSESSMENT IN THE UNITED STATES

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In the United States, probabilistic risk of dietary risk has been practiced since before 1996. However, the passing of the Food Quality Protection Act (FQPA) in August of 1996 spurred additional research into the use of probabilistic techniques, including residential, aggregate and cumulative exposures. The current discussion will focus on the use of probabilistic techniques for addressing dietary risks.

FQPA was a significant impetus for advanced techniques of exposure analysis, in part because of FQPA's mandate for additional uncertainty factors when considering potential risks to children. FQPA furthermore requires that all tolerances be re-evaluated according to the revised FQPA standards within 10 years of the passing of the Act. Among these new standards are considerations of aggregate and cumulative exposures.

With FQPA, the US Congress directed that the Environmental Protection Agency (EPA) confirm that the US population, particularly children, were not at risk from pesticide residues through different routes (oral, dermal, and inhalation) or in combination with other chemicals having a similar mechanism of toxicity. At the time FQPA was passed, the EPA did not have the technology to perform such assessments. Consequently, the EPA developed a series of science policy papers. These papers have been under development since approximately mid-1997, with some of them being written as recently as two months ago. The science policy areas are 1) applying the 10-fold FAPQ safety factor, 2) dietary exposure and the 99.9th percentile issue, 3) interpreting samples without detectable residues, 4) a user's guide for dietary exposure estimates, 5) drinking water exposures, 6) drinking water screening level assessments, 7) assessing residential exposure, 8) aggregating exposures from all non-occupational sources, 9), cumulative risk, an 10) selecting an appropriate toxicity endpoint for evaluating the organophosphate insecticides. In addition, the EPA published supplemental papers to expand on these areas. It is clear from this list of policy areas, that the EPA adopted a quantitative risk assessment approach to deal with the requirements of FQPA.

Dietary risk is a function of the amount of food consumed and the residue level on that food. This relationship defines dietary exposure. The risk assessment is "created" when the exposure estimate is compared to some measure of toxicity. Exposure may be evaluated in two general ways. Chronic, or long-term, exposure is evaluated using estimates of long term food consumption patterns and typical residue values. The resulting point estimate of mean exposure is compared to the acceptable daily intake, ADI. In contrast to chronic exposure, acute, or short-term, dietary exposure can also be evaluated. The acute dietary risk assessment considers daily individual food consumption patterns and the residues that occur on the food that is consumed. The acute risk assessment considers the entire distribution of exposure, even if the approach is not probabilistic. The non-probabilistic risk assessment assumes uniform residue levels in the entire food supply, but a distribution of exposure is created from the variation in food

consumption. The magnitude of the dietary exposure estimate at a sentinel percentile, such as the 95th or 99.9th percentile, is compared to an acute reference dose.

What do we mean by acceptable risk? Simply, if the exposure estimate is less than the toxicity endpoint, the risk is considered acceptable. If the exposure is greater than the toxicity endpoint, the risk is considered unacceptable.

There are two basic approaches to modeling exposure. In the deterministic approach, point estimates of the model inputs (consumption and residue concentration) are used to calculated a point estimate of exposure. In the distributional approach, the input variables are provided as distributions of values. The probabilistic approach is a refinement of the distributional approach in which the likelihood of an input value being sampled is based upon its probability of occurrence. The probabilistic approach is also called the Monte Carlo approach.

Probabilistic dietary risk assessments require a large amount of data, starting with data for food consumption. In the United States, the food consumption data is provided by the Continuing Survey of Food Intake by Individuals (CSFII). This food consumption survey was designed to be representative of the US population, as well as various population sub-groups, categorized according to geographic area, ethnic group, age, gender, and season of sampling.

As thorough as a food consumption survey such as the CSFII is, it can only approximate actual food consumption patterns. Food consumption data may be collected using a food intake record, a food intake recall, or a food frequency questionnaire. The CSFII uses the food intake recall technique. Other surveys, such as the surveys conducted in the UK, use the food intake record technique. One of the most significant aspects of using food consumption data for risk assessment purposes is that the consumption data are collected in the form in which the foods are consumed. However, the risk assessment typically is conducted using raw agricultural commodities (RAC). Therefore, the food consumption data in the CSFII must be translated to RACs. The CSFII food consumption database provides data suitable for a Monte Carlo risk assessment.

Residue concentration is the other part of the exposure equation. In deterministic assessments, one value is assumed for the assessment. In a probabilistic assessment, residues are sampled from the residue distribution. The residue concentration can also be modified by the effects of processing and by the percent of the crop that is treated. In the United States, the use of percent crop treated in the probabilistic assessment is an extremely powerful tool for mitigating the magnitude of the exposure estimate. In the US model, zero residues are assumed in proportion to the percent of the crop that is treated. Since exposure is a product of food consumption and residue, whenever a zero residue is sampled, the resulting exposure estimate is also zero.

In practice, the EPA considers 4 Tiers of acute dietary assessments. Tiers 1 and 2 provide for distributional, but non-probabilistic, assessments. The EPA Tier 3 assessment is the basic probabilistic assessment in which samples are drawn from the

residue distribution. In the Tier 4 assessment, residue data from individual samples, such as individual apples or oranges, are used in a probabilistic assessment.

To a certain extent, the probabilistic assessment practiced by the EPA is a hybrid, because a true probabilistic assessment would randomly sample from both the food consumption and residue distributions. Although the model used by the EPA samples from the residue distributions, it uses all of the food consumption information available.

In a simple case study for apples and peaches, the EPA Tier 1 assessment resulted in an exposure estimates at the 99.9^{th} percentile that ranged from 130% to 196% of the acute RfD. A probabilistic assessment that assumes 100% of the crop treated resulted in reduced the risk estimate somewhat, ranging from 76% to 169% of the acute reference dose. Finally, incorporating percent crop treated in the assessment resulted in a total dietary exposure estimates ranging from 37% to 115% of the acute reference dose. This simple test case demonstrates the extent to which the probabilistic assessment can change the results of the assessment with relatively simple data, but also shows that the probabilistic approach does not hide potential high residues, but rather places them in the proper context.

The EPA has been using probabilistic techniques to assess dietary risks for several years. Recently, they used probabilistic techniques to an assessment of cumulative risk for the organophosphate insecticides. One of the key features of the EPA's cumulative risk assessment was the use of regional data with respect to exposure from drinking water. Regarding the dietary portion of the exercise, the EPA's cumulative risk assessment for the organophosphate insecticides indicated that acceptable exposure levels were exceeded above the 99.5^{th} percentile for children.

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APPENDIX III: ABBREVIATIONS USE IN THE TEXT

ACPH	Advisory Committee on Pesticides and Health
ACT	Australian Capital Territory
ADI	Acceptable Daily Intake
AFFA	Agriculture, Fisheries and Forestry – Australia
ANZFA	Australia New Zealand Food Authority
ARfD	Acute Reference Dose
CCPR	Codex Committee on Pesticide Residues
DHAC	Department of Health and Aged Care
DIE	Dietary Intake Estimate - An estimate of chronic dietary intake based on a combination of STMRs and MRLs
ECRP	Existing Chemical Review Program, conducted by the NRA
EU	European Union
FAO	Food and Agriculture Organisation
GAP	Good Agricultural Practice in the use of pesticides (label directions)
GRDC	Grains Research & Development Corporation
IEDI	International Estimated Daily Intake
IESTI	International Estimated Short-Term Intake
IPM	Integrated Pest Management
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	Lowest Observable Adverse Effects Level
MRL	Maximum Residue Limit
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
NRA	National Registration Authority for Agricultural and Veterinary Chemicals
NRS	National Residue Survey
PHI	Pre-Harvest Interval
STMR	Supervised Trials Median Residue
TGA	Therapeutic Goods Administration
TMDI	Theoretical Maximum Daily Intake
WHO	World Health Organization