Zumbiehl Janine CHBS

From: Sullivan Jonathan Dale CHBS
Sent: Dienstag, 15. Juli 2008 10:01
To: jwolff@fulbright.com; Nadel Alan USGR
Cc: Maeder Christoph CHBS
Subject: PARAQUAT
Attachments: draft notes.doc; 080619 draft minutes.doc

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Jeff and Alan,

I attach for your review and comments two sets of draft Minutes or Notes of Internal meetings relating to paraquat, including draft enclosures, which I received yesterday .

The first set of draft Minutes records a Meeting of the "Inteon" Science and Regulatory Team held on 19 June to review the sequence of disclosure meetings held in April and May with applicable regulatory authorities and to consider the study program ar related with future formulation strategy . In the latter area the Minutes appear to evince an interest in changing, in relation to n formulations, the approach to testing for acute oral toxicity and to suggest that only rat and not dog studies would be carried out . In addition a question is raised as to the minimum level of testing which would be required from a regulatory perspective to demonstrate that a new formulation is of equivalent safety to "Inteon" .

The second document is a set of draft Notes of a joint meeting of the Product Safety and Global Product Regulation teams held to consider the risk assessment in relation to operator exposure, based on the published experimental studies, which it was agreed by the Issue Leadership Team on 16 April 2008 should be carried out by Product Safety in accordance with their regulatory duty of care .

The risk assessment is at least for me as a non-scientist quite difficult to follow and I have put in a call to John Doe with a view to having him explain it to me . The conclusion appears to be that the predicted NOEL for neuronal cell loss in humans which can be extrapolated from the mouse studies is about 50 times higher than the current regulatory reference dose of 0.0005 mg/kg/d . However it is accepted that there is significant uncertainty around these predictions which could only be resolved through further studies . There are a number of statements in the paper which taken out of context would potentially be unhelpful .

Jor an .

16.07.2008

Botham, Philip
Exhibit_95
6/19/2020

Phil Botham
Angela Brady
Andy Cook
Roland Dieterle
John Doe
Kersten Mewes

10th July 2008

Draft notes from PS/GPR meeting
On 10th July 2008

1. Assessment of the operator exposure reference dose in light of emerging data

The following draft Product Safety evaluation of the reference dose was reviewed.


Draft PQ Parkinsons
Draft Reference Dose

Clarifications of specific points during the discussion lead to the following executive summary which will be included in the next version of the PS document.

- The one consistent finding in animal studies is the loss of dopaminergic neurones in the substantia nigra C57BL6J mice.
- This finding is judged to be real, to be related to treatment and to be adverse in nature
- In the absence of evidence to the contrary, it is prudent to assume that this finding is potentially qualitatively relevant to man
- The ip dose route is not a relevant route of exposure and therefore requires route-to-route extrapolation
- Nevertheless, we should check whether these findings would change the reference dose for operators
- In absence of data from a study of appropriate type and duration, we should try to estimate a reference dose using a number of assumptions, each with associated uncertainty
- Although the estimated reference dose is approximately 2-fold lower than the current Syngenta reference dose position, given the uncertainty of the calculation Product Safety considers the difference not to be significant
- 2007 have independently concluded using a PBPK model that there is likely to be a substantial margin of safety for operators via the dermal route
- The robustness of the conclusions from both Product Safety and McIntosh & Kedderis would benefit from the generation of more relevant data to remove some of the levels of uncertainty. These data should still be generated in the C57Bl6 mouse in the absence of evidence regarding relevance to man of effects seen in this strain, which should also be investigated
- Given the big margins of safety for dietary exposure, there are no concerns for safety to consumers
- There is no evidence that the foetus is more susceptible to this effect.

2. Preliminary regulatory assessment

With the clarifications given in the above executive summary, a preliminary regulatory assessment was presented. This will need further discussion with the regulatory team.

- Lack of robustness of assessment:
  - The database is not suitable to derive a NOEL and reference dose for operators with regard to the effects seen in the brain of the C57Bl6J mouse.
  - There are many assumptions with associated uncertainties
- We would not use this assessment with regulators as it is not robust:
  - The estimate of the reference dose is only weakly supported by data and we might get criticism
  - Regulators would rather use additional safety factors (eg in absence of NOEL apply an extra safety factor of 3 to the ip LOEL of 1mg/kg: Add extra 10 fold uncertainty factor ie 1000 instead of 100: no modification for absorption as ip is a systemic dose; therefore check AOEL would be 1 / 3 /1000 = 0.00033 mg/kg/day, which is not dissimilar to proposed)
  - Regulators could make their own assessment using the published data
  - New/future data (own or by others) may show conclusions from the estimate to be wrong
  - The generation of a suitable set of new data is needed and can be done; some could be done at a reasonable effort (eg TK)
- Continue to move quickly to avoid the risk to be seen to act slowly
- Prudent to assume that the effects on substantia nigra will be interpreted by some regulatory authorities as indicative of neurotoxicity and this needs clarification
- Continue with planned program to generate new data
  - Compare different routes of exposure (ip, gavage, dietary, intranasal); single vs multiple (steady state) – consider DEFRA data
  - Use appropriate route for effect studies (dose/response, NOEL)

3. Further points requiring clarification

There are some points in the various internal texts produced over time which are unclear when read side by side. It was agreed that these should be reviewed in detail by Product Safety/Registration and an up to date text produced.

4. Update on PK studies

PAB reported that the prelim (method evaluation) study will be conducted at Charles River, Scotland, in collaboration with Xceleron, York. Enabling work has already started. Details of main kinetics study have not been finalised and will be subject to further debate at the next Science Team meeting on July 30th (particularly on dose level selection), and on outcome of prelim.

At this time, it is assumed that for operator reference dose the NOEL for effects on substantia nigra in C57Bl6 mice will be determined by the dietary route. Although the dietary route is not strictly relevant to operator exposure for Pq, this is considered to be the most robust experimental approach for a study of this type.

Further discussion on the design of this study must await establishment of the methods for the substantia nigra effects in the conducting laboratory and the preliminary kinetics studies may guide dose level selection.

Actions

1	Find out if we have a document which can be used to easily reference our position on dietary residues and margins of safety. (If not, we will produce it)	RD/AC	End August(End Oct)
2	To further refine the regulatory assessment a retrospective timeline needs to be created of when key internal and published studies were conducted and conclusions reached and whether these were included in regulatory submissions	AC/RD	End August
3	Review the precise wording in the key Syngenta study and regulatory submission documents in 2. above and advise on whether the wording correctly describes our understanding at the time and today. • regarding whether Pq distributes into the brain • regarding whether Pq accumulates or is persistent in the brain • regarding whether the effects on the substantia nigra should be interpreted as being indicative of neurotoxicity	AC/RD	End August
4	Develop the design of the studies specifically needed for establishment of NOEL for substantia nigra effects for operator exposure reference dose	Science Team	July 30th meeting

Privileged & Confidential – Attorney Work Product

PRODUCT SAFETY TECHNICAL EVALUATION

Claimed Links Between Exposure to Paraquat and Development of Parkinson's Disease

A Re-evaluation of the Reference Dose Used in the Assessment of Risk to Operators and Comment on Implication for Consumer Risk Assessment

Draft Version 2

Background - Animal Studies of Paraquat and Parkinson's disease

The principal animal model devised for investigative research into the possible association between exposure to paraquat and the development of Parkinson's disease (PD) involves the $C_{57}Bl_{6J}$ strain of mouse (young males 8-12 weeks of age), and multiple (typically three doses) i.p. administrations of paraquat. The doses used are up to 10 mg/kg, which approximates to a significant fraction (one third) of the median lethal dose (Lock & Wilks, 2001). The main toxicological endpoints are neuronal cell number in the substantia nigra *pars compacta* brain region as determined by stereology, biochemical changes in the striatum region of the brain (dopamine concentration) and behavioural changes such as locomotor deficits.

A number of laboratories, including Syngenta CTL, have observed a reduction in neuronal cell counts of dopaminergic neurones in the substantia nigra *pars compacta* brain region following paraquat administration utilising a dosing regimen of 10 mg/kg paraquat (dichloride salt) once or twice a week for three weeks (McCormack et al., 2002; Barlow et al., 2004; Cory-Slechta et al., 2005; CTL report no. XM7258/Research/Report). The reduction in neuronal cell counts appears to be limited to approximately 25-30%, even on increasing length of dosing, and there is some evidence for oxidative damage being involved in the neurones affected (McCormack et al., 2005; 2006). A dose response for neuronal cell loss has been reported utilising this 3x weekly i.p. dosing regimen, with 1, 5 & 10 mg/kg paraquat giving rise to 10, 18 & 28% neuronal cell loss respectively (McCormack et al., 2002). The neuronal cell loss appears to be restricted to the substantia nigra *pars compacta* brain region as no reduction in cell counts is reported in other dopaminergic brain areas such as the ventral tegmental area and hippocampus. Furthermore, the reports of the nigrostriatal deficits occur at paraquat doses which do not lead to any lung, kidney, heart or liver pathology (Thiruchelvam et al., 2000a; Barlow et al., 2004).

The reports of a reduction in striatal dopamine concentration are mainly from one laboratory (Brooks et al., 1999) and have not been replicated by others, including Syngenta CTL. The same research group reported behavioural changes, which like the dopamine changes, have not been reproduced in other laboratories, including Syngenta CTL (CTL report no. XM7371/Research/Report). The changes observed in this model are therefore not the complete range or sequelae consistent with PD symptoms in humans.

There have been some limited reports of effects of paraquat in a similar rodent model, namely in the rat (Cicchetti et al., 2005; Ossowska et al., 2005). The duration of paraquat exposure and total dose administered was reported to be greater to achieve similar deficits as in the mouse model, indicating the rat may be less sensitive. However, there is evidence that these findings are again not reproducible in other laboratories, such as our own, where we observed no neuronal cell count or striatal dopamine content deficits following i.p. administration of 10 mg/kg paraquat twice a week for 4 weeks (Syngenta CTL report no. XR7641/Research/Report).

A number of publications from one particular research group have indicated a possible synergistic effect of paraquat and the fungicide maneb when applied to the $C_{57}Bl_{6J}$ mouse model system (Thiruchelvam et al., 2000a & b; 2002; Cory-Slechta et al., 2005). Repeated i.p. doses of 0.3-10 mg/kg paraquat and 1-30 mg/kg maneb to neonates and adult mice produced neuronal cell loss and neurochemical changes (dopamine reduction) in the substantia nigra and striatum respectively that were greater in magnitude than with either the same doses of paraquat or maneb alone.

Further studies conducted with this mouse model by this same research group suggest that the neonate appears to be more vulnerable to paraquat and maneb exposure (Thiruchelvam et al., 2002; Cory-Slechta et al., 2005). In a complex experimental protocol, mice were injected daily through the i.p. route with either paraquat (0.3 mg/kg), maneb (1 mg/kg) or with the combination of paraquat and maneb, from post-natal days 5-19 (total of 15 doses). A subset of these mice was then exposed as adults twice a week for 3.5 weeks (7doses) to paraquat (10 mg/kg), maneb (30 mg/kg) or a combination of paraquat and maneb. Exposure to the paraquat and maneb combination as a neonate and as an adult produced greater nigrostriatal and locomotor deficits than those animals exposed as neonates or as adults only.

This same research group has recently (2007) reported in a poster presentation that a dose of 0.1 mg/kg/day paraquat i.p. on post-natal days 5-19, either alone or in combination with 1 mg/kg/day maneb, can lead to nigrostriatal deficits which do not become apparent until the animals reach an age of >18 months. These deficits are greater in magnitude and become apparent at an earlier age in those animals that had the combination exposure. These effects seem to be gender related (see below), with females being affected to a lesser extent.

An extension to these developmental studies with maneb and paraquat has been reported where pregnant mice dams were dosed with 1 mg/kg/day maneb s.c. on gestational days 10-17 and the subsequent off-spring (at an age of 45 days) then exposed to 30 mg/kg maneb or 5 mg/kg paraquat i.p. each day for 8 consecutive days (Barlow et al., 2004; Cory-Slechta et al., 2005). The prenatal exposure to maneb had no significant impact on the extent of the magnitude of the toxicity endpoints observed as a result of adult exposure to maneb, whilst it significantly reduced locomotor activity, striatal dopamine and nigral neuronal cell counts in the paraquat exposed adults. On the other hand, pre-natal exposure to paraquat (0.3 mg/kg/day s.c.) on gestational days 10-17, did not lead to nigrostriatal deficits (including neuronal cell loss), when exposed to maneb as young adults.

There are some reports that indicate there are gender-related differences in the paraquat and maneb exposure animal model, with male mice being more susceptible than females (Thiruchelvam et al., 2005; Cory-Slechta et al., 2005) however this has not been uniformly reported by all research groups using the model.

Product Safety Evaluation of the Animal Studies

The one consistent finding from the body of animal studies is the loss of dopaminergic neurones in the substantia nigra *pars compacta* of male $C_{57}Bl_{6J}$ mice. This finding is judged to be real, to be related to paraquat treatment, and to be adverse in nature. It is not clear if neuronal cell loss in response to paraquat exposure is peculiar to this particular mouse model, but in the absence of evidence to the contrary, it is prudent to assume that this finding is potentially relevant to man. Therefore, a re-evaluation of the reference dose used in risk assessments has been conducted and is documented below. For the purpose of this re-evaluation, it has been judged that the evidence for a reduction in striatal dopamine and for locomotor deficit is less clear. If such effects do occur in this mouse model then they are assumed to be secondary to neuronal cell loss, and therefore a reference dose and subsequent risk assessment based on neuronal cell loss would also protect against such potential effects. If there are any similar effects in the rat, which is currently doubtful, then they occur at higher doses and would also be covered by the selection of a reference dose and risk assessment based on neuronal cell loss in the $C_{57}Bl_{6J}$ mouse.

Re-evaluation of Reference Dose for Operator Risk Assessment

Although neuronal cell loss in the $C_{57}Bl_{6J}$ mouse is currently assumed to be relevant to man, the intraperitoneal (i.p.) dose route used in these studies is clearly not relevant to human exposure. The main routes of potential exposure of spray applicators to paraquat are the dermal and inhalation routes. The risk assessment for applicators is currently based on a 90 day dietary study in the dog, with a no-effect level (NOEL) of 0.55 mg/kg/d (Sheppard, 1961), typically rounded down by regulators to 0.5 mg/kg/d. From this NOEL, a reference dose (an acceptable operator exposure level, AOEL) is derived as follows

AOEL = (NOEL x fraction oral absorption / safety factor)

AOEL = 0.5 x 0.10 / 100

= 0.0005 mg/kg/d

This calculation uses a default fractional oral absorption of 0.1. Syngenta's technical view of a more appropriate AOEL estimate would be to use an unrounded NOEL, and a fractional oral absorption of 0.13 from a dog oral bioavailability study (CTL Report UD0936/Regulatory/Report), resulting in an AOEL of 0.0007 mg/kg/d, but the lower value of 0.0005 forms the basis of paraquat regulation.

The selection of reference dose and assessment of risk to applicators is based on a dietary endpoint, and therefore it is necessary to estimate a dietary NOEL for neuronal cell loss in the $C_{57}Bl_{6J}$ mouse and to compare this to the currently used AOEL reference dose. Many steps are involved in estimating a dietary NOEL for

neuronal cell loss from the existing data, and each has its own uncertainties and assumptions. The approach adopted here is to seek to estimate the most likely value for the dietary NOEL, and to give an indication of the uncertainties that surround this single value. The following paragraphs outline the steps involved.

As stated earlier, a dose response for neuronal cell loss has been reported utilising a 3x weekly i.p. dosing regimen, with 1, 5 & 10 mg/kg paraquat giving rise to 10, 18 & 28% neuronal cell loss respectively (McCormack et al., 2002). There was no NOEL in this study, but the lowest dose is probably close to a NOEL, given the variability inherent in such studies. Therefore it will be assumed that three weekly doses of 0.5 mg/kg by the i.p. route would be a NOEL.

It has been established that the great majority of neuronal cell loss with weekly i.p. doses of 10 mg/kg occurs within a three day window (McCormack et al, 2005), which is consistent with the cell loss being triggered when a certain brain concentration is reached. Therefore the maximum concentration of paraquat in the brain is presumed to be an appropriate dose metric for the endpoint of neuronal cell loss. Neuronal cell loss is presumably driven by the local concentration of paraquat. However, studies to date do not indicate that the concentration in the affected region is different from the whole brain concentration (see for example Naylor et al, 1995; CTL Report UM0924/General/Report; Macintosh et al, 2008) and therefore maximum whole brain concentration of paraquat is used here as the dose metric. The maximum concentration of paraquat in the brains of $C_{57}Bl_{6J}$ mice following 3x weekly i.p. doses of 1 and 10 mg/kg are 0.05 and 0.50 ug/g respectively (CTL Report UM0924/General/Report). Dose linearity in this study was excellent, therefore the maximum concentration of paraquat in the brain at the assumed NOEL is estimated to be 0.025 ug/g.

The next step is to estimate the single ip dose that would result in this concentration of paraquat in the brain. A single 10 mg/kg ip dose resulted in a maximum paraquat concentration in brain of 0.22 ug/g (CTL Report UM0924/General/Report), therefore it is presumed that a single i.p. dose of 1.1 mg/kg (10 x 0.025 / 0.22) would result in a maximum brain concentration of 0.025 ug/g. McIntosh & Kedderis (2007) measured concentrations of paraquat in the brains of $C_{57}Bl_{6J}$ mice following single 10 mg/kg doses of paraquat by the i.p. and oral gavage routes, the resulting concentrations being approximately 0.25 and 0.035 ug/g, respectively. Therefore the single oral dose resulting in the same paraquat brain concentration as that occurring at the assumed NOEL can be estimated to be 8.1 mg/kg (1.1 x 0.25 / 0.035). The plasma profile during a dietary study would be quite different from that by oral gavage, but in the absence of evidence it is assumed that oral gavage and dietary routes are equivalent in terms of brain loading. Therefore the single day dietary dose resulting in the same paraquat brain concentration as that occurring at the assumed NOEL is estimated to be 8.1 mg/kg.

Paraquat is quite persistent in the brains of $C_{57}Bl_{6J}$ mice, with a half-life of about 21 days (derived from CTL Report UM0924/General/Report; also see Prasad et al, 2007). Assuming simple exponential kinetics, the average paraquat concentration at steady-state is the concentration after a single day of dosing multiplied by the half-life divided by the natural log of 2. Therefore the chronic dietary dose which results in a steady-state paraquat brain concentration which is the same as that occurring at the assumed NOEL is estimated to be 0.27 mg/kg/d (8.1 x ln(2) / 21). This is the estimated chronic dietary NOEL for neuronal cell loss in the $C_{57}Bl_{6J}$ mouse. This is a

factor of two lower than the current 90 day dog NOEL. Assuming a fractional bioavailability for the dietary route of 0.1 in the $C_{57}Bl_{6J}$ mouse, this is equivalent to a systemic dose of 0.027 mg/kg/d, which is about 50 times higher than the regulatory AOEL reference dose of 0.0005 mg/kg/d. The implication for pesticide applicators is that exposure at the regulatory AOEL, which by definition is the upper limit on acceptable operator exposure, is about 50 times lower than the NOEL for neuronal cell loss in the $C_{57}Bl_{6J}$ mouse. This factor of 50 represents a realistic point estimate of the safety margin.

In addition to point estimates it is important to convey the level of uncertainty associated with the estimates. Calculations have been performed using a reasonable set of assumptions about the uncertainties in each step. The major sources of uncertainty in decreasing order of influence were found to be:

- the uncertainty of the NOEL in the three dose i.p. model,

- the uncertainty in the brain loading from a single oral dose,

- the uncertainty of persistence in the brain,

- the uncertainty in the relative brain loading from dietary vs oral dosing.

The uncertainty calculations resulted in 95% confidence limits for the chronic dietary NOEL of 0.08 to 0.77 mg/kg/d, which equate to a systemic dose which is 16x to 154x greater than the regulatory AOEL.

Further uncertainties are associated with whether the calculation used is the right one; this is called model uncertainty, and is harder to quantify. Uncertainties in this category include:

- the possibility that the lesion may progress in the long-term, even without further dosing, as has been demonstrated following neonatal dosing,

- the possibility that the lesion may not be driven by the Cmax, but by the AuC over some time-period,

- the possibility that whole brain paraquat concentration may be a poor surrogate dose metric for the relevant local concentration of paraquat in the brain, because the kinetics of the relevant local concentration do not exactly follow those of the whole brain,

- the possibility that oral and dietary kinetics may be non-linear with respect to dose (unlike ip dosing kinetics, which is linear).

McIntosh & Kedderis (2007) used a completely different approach to that adopted in this document, theirs being based on a physiologically-based pharmacokinetic model. They concluded that applicators would be exposed to 6 to 8 orders of magnitude less paraquat than mice in the standard model dosed 3x 10 mg/kg paraquat i.p.

Ideally, selection of an appropriate reference dose and subsequent risk assessment would not be driven by effects in the $C_{57}Bl_{6J}$ mouse alone, but would include an understanding of strain and species differences, and of the mechanism of toxicity of paraquat in this model system. This would result in an understanding of the relevance and applicability of these findings to man, considerably reducing the uncertainty of the risk assessment. However, the scientific understanding necessary to support such a human risk assessment does not currently exist.

Comment on Implication for Consumer Risk Assessment

Consumer risk assessment for paraquat is based on consumption of food which might contain residues of paraquat. Since residues of paraquat on agricultural commodities are rarely detected, the maximum residue levels (MRLs) for most crops in most countries are set at the limit of quantification (LOQ) of the residue analytical method. Even assuming that residues of paraquat may be present at the MRL, regulatory consumer risk assessments for paraquat typically have large margins of safety, larger than the required 100x minimum. A recent market-basket survey in the US was focussed on the commodities contributing most to exposure in consumer risk assessments (Syngenta Report T002949-03), and used a very sensitive analytical method with an LOQ ranging from 0.0015 to 0.0024 mg/kg. Paraquat was only above the LOQ in 7 samples out of 2100. There were no residues above the LOQ in apple juice, bananas, beer, grapes, milk or canned pineapple. All seven samples above the LOQ were potatoes, with a maximum value of 0.068 mg/kg, which is considerably below the US MRL of 0.5 mg/kg. From these data it is clear that dietary exposure to paraquat is negligible. Therefore any modest reduction in the dietary NOEL for paraquat would have no consequence for safety to consumers.

Other Issues of Possible Relevance to the Selection of a Reference Dose for Risk Assessments

Exposure to Early Life Stages

Mice exposed on postnatal days 5 to 19 appear to be more sensitive to neuronal cell loss induced by paraquat than the young adult mice used in the standard model (the data are reviewed earlier in this document). A given paraquat i.p. dose results in a higher paraquat concentration in the blood and brain of juvenile animals compared to adults (McIntosh & Kedderis, 2007), and this accounts for most, if not all, of the sensitivity difference. Given that dietary exposure to paraquat is negligible, this does not cause a concern regarding consumer risk assessment. In addition, pesticide applicator risk assessment is not relevant for this age-group. However, the reported finding that early postnatal exposure resulted in an initial neuronal cell loss which increased much later in life is an important one. The implication is that definitive studies seeking to establish an NOEL for neuronal cell loss, irrespective of age at dosing, may also need to be continued for a long time in order to give any lesion the opportunity to fully develop.

Intranasal/Inhalation Exposure

McIntosh & Kedderis (2007) showed for the first time that dosing by an intranasal route results in higher brain concentrations than by the i.p. route. It is currently unclear precisely how the dosing was done, and whether it can be considered relevant to the human situation. The mechanism of transfer from the nose to the brain is also unclear, except that it is mainly not via the blood (McIntosh et al, 2008). The reported intranasal kinetics of paraquat is of considerable interest, and Syngenta is seeking to obtain further information on what was done as a matter of course, so that any implications can be properly evaluated, including the potential need for a risk assessment for human exposure via this route.

Conclusions

In conclusion, the best current prediction of the chronic dietary NOEL for neuronal cell loss in the male $C_{57}Bl_{6J}$ mouse is 0.27 mg/kg/d. This is a factor of two lower than the current chronic NOEL of 0.55mg/kg/d. Assuming a fractional bioavailability for the dietary route of 0.1, the predicted NOEL is equivalent to a systemic dose which is about 50 times higher than the regulatory AOEL reference dose of 0.0005 mg/kg/d. This factor of 50 represents a realistic point estimate of the safety margin for pesticide applicators exposed at the AOEL. There are considerable uncertainties in these predictions, and the major sources of uncertainty have been outlined. Consumer dietary exposure to paraquat is negligible, and consumer safety is not expected to be under threat from any modest change in the chronic NOEL. The significance of intranasal dosing studies for the human situation cannot yet be determined.

Nick Sturgess , Kim Travis and Phil Botham
16th June 2008

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