UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 2 1994

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Acute and Chronic Dietary Exposure Analyses for DDVP

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TO: Dennis Utterback, Review Manager
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and

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THROUGH: Elizabeth A. Doyle, Head E.A. Doyle
DRES/SAB
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Action Requested

Special Review Branch has requested Dietary Risk Evaluation System (DRES) estimates of acute and chronic risk (including cancer risk) from dichlorvos (DDVP), both from the use of dichlorvos itself as well as from the use of naled, of which DDVP is a degradate. The risk estimates provided are to be used in the PD 2/3 for the DDVP Special Review.

Discussion

1. Toxicological Endpoints

a. **Chronic non-cancer:** chronic exposure in these analyses was compared to a Reference Dose (RfD) of **0.0005 mg/kg bwt/day**, based on a No Observed Effect Level (NOEL) of 0.05 mg/kg bwt/day and an uncertainty factor of 100. The NOEL was taken from a 1 yr. feeding study in dogs in which plasma and red blood cell cholinesterase inhibition (ChE) were the effects observed in males and females; in addition, brain cholinesterase inhibition was observed in males (G. Ghali memorandum to G. LaRocca and L. Rossi dated 6/10/92).

b. **Cancer:** DDVP has been classified as a Group C possible human carcinogen by the HED Carcinogenicity Peer Review Committee (G. Ghali to G. LaRocca, 9/18/89). In accordance with the policy outlined in P. Fenner-Crisp's memorandum of 7/1/94 to B. Burnam, H. Pettigrew and K. Dearfield, the upper bound potency factor (Q_1*) for DDVP was revised to incorporate the 3/4 interspecies scaling factor. The revised Q_1* is **1.22 x 10^{-1} (mg/kg/day)$^{-1}$** (B. Fisher and H. Pettigrew memo to D. Edwards, 9/20/94); the previous Q_1* was 2.0 x 10^{-1} (mg/kg/day)$^{-1}$.

c. **Acute:** high end exposure in the DRES acute analyses was compared to a NOEL of **0.5 mg/kg/day** for signs associated with ChE inhibition, taken from an acute neurotoxicity study in rats (M. Beringer memorandum to D. Utterback, 9/8/93). As this chemical has not yet been evaluated by OPP's Less Than Lifetime Committee, there has at this time been no official recommendation on the appropriateness of this endpoint for acute dietary risk assessment, or on the appropriateness of characterization of acute dietary risk from DDVP; this NOEL was used to calculate acute Margins of Exposure (MOEs) for occupational and residential exposure in the aforementioned Beringer memo, and was informally acknowledged as the most appropriate endpoint for acute dietary risk by E. Doyle, secretary of the Less Than Lifetime Committee (personal communication w/ E. Doyle, 11/28/94).

2. Residue Information

This risk assessment consists of two analyses which evaluated DDVP residues from the use of DDVP itself as an insecticide and from the use of naled, of which DDVP is a metabolite. DDVP residues from trichlorfon, another related organophosphate which forms DDVP metabolites, were not considered in this analysis at the recommendation of CBRS; registered uses of trichlorfon generally stipulate PHIs of a greater time duration than DDVP residues are found to exist (F. Suhre memorandum to A. Schmidt dated 4/28/88). The consideration of naled-derived DDVP in the DDVP Special Review risk assessment was recommended in Suhre's 4/28/88 memo.

Food uses evaluated for DDVP were the published uses listed in 40 CFR 180.235 and 185.1900, and in the Tolerance Index System (TIS). Tolerance expressions listed in the CFR for bagged or packaged non-perishable processed foods and raw agricultural commodities (RACs), including bulk stored RACs, are ill-defined as to which specific commodities or processed forms of commodities should be considered as possibly containing residues of DDVP through the uses that these tolerances cover. The data file used in this analysis represents the historic interpretation of what commodities might be exposed to DDVP through any one of these tolerances. As support for a draft Notice of Intent to

Cancel, CBRS did provide its interpretation of which commodities in the DRES file it felt to be processed and which additional commodities should be considered for dietary risk assessment (D. McNeilly memorandum to K. North, 8/14/91); this list of RACs is included in a J. Kariya memorandum to M. Beringer dated 8/23/91. There has been no tolerance specific determination of the universe of commodities which might receive residues from the tolerances for "non-perishable bulk stored RACs", "bagged or packaged non-perishable RACs having greater than 6% fat", and "bagged or packaged non-perishable RACs having less than 6% fat".

It should be noted that because these tolerances were established to cover residues resulting from use of DDVP at different sites and were not made commodity specific, some RACs in the DRES file are likely to contain residues of DDVP applicable to more that one of these tolerances. That is, more than one of the tolerances in 180.235 may apply to certain RACs in the DRES file. One implication of this situation is that cancellation of any one of these site specific uses does not necessarily eliminate risk from a given RAC to which the tolerance for that use is applied. Additivity of residues between sites was not considered in creating the anticipated residues, but was considered in the percent of crop treated estimates for DDVP.

The following commodities were added to the DDVP file for this analysis, all through the published tolerances for DDVP on either "non-perishable, bagged or packaged processed commodities" or "raw agricultural commodities, non-perishable, bulk stored":

dates	herbs and spices
figs	hops
popcorn	

Dried citrus and small fruits and berries were also recommended by CBRS for inclusion in the DRES file, but were not added because DRES does not have consumption estimates for the dried forms of these crops. "Potatoes", "carrots" and "onions" were considered as possibly being non-perishable, but excluded from the analysis on the grounds that the DDVP label specifically states that "vegetables such as onions, parsnips, potatoes and carrots" are not to be considered as non-perishable raw agricultural commodities.

It should be noted that while DDVP is registered for use in food handling establishments (U.S. EPA, Guidance for the Reregistration of Pesticide Products Containing DDVP as the Active Ingredient, 9/87), there is no accompanying tolerance supporting this use. For this reason, the possibility of residues on foods due to DDVP use in food handling establishments was not considered in this analysis. **If DDVP is in fact being applied in food handling establishments, this is a probable source of underestimation of dietary risk in this analysis.**

The naled food uses evaluated were those listed in 40 CFR 180.215 and in TIS. Every food commodity in DRES was included in the "DDVP from naled" file, due to a tolerance of 0.5 ppm which covers residues resulting from the use of naled as an area mosquito and fly control; the tolerance expression specifies that the tolerance is applicable to all RACs except those already listed as having individual tolerances in 180.215. Although the possibility exists that DDVP residues could occur on any given RAC from this use of naled, it remains unlikely that residues would be found on all RACs; this presents a probable source of overestimation of exposure and risk in the chronic and acute analyses.

Percent crop treated refinements: Percent of crop treated (PCT) information for both DDVP and naled was supplied by BEAD in a J. Faulkner and D. Sutherland memorandum to D. Edwards dated 10/26/94. Subsequent questions and clarifications regarding this memo are discussed in a Schaible note to Faulkner and Sutherland dated 10/26/94 and their response dated 11/2/94. Where a range of percent crop treated values were supplied, the upper end of the range was assumed. The following are the more significant assumptions made for each chemical.

a. **DDVP**: Although no quantitative estimates of percent of crop treated were given for the agricultural sites of DDVP (radishes, mushrooms, cucumbers, lettuce, and tomatoes), it was assumed that less than one percent of these crops has DDVP residues on them from agricultural use. The tolerances for DDVP on radishes, cucumbers, lettuce, and tomatoes were established to cover residues of DDVP occurring through use of naled; therefore naled PCT estimates supplied for these crops were applied to the DDVP file as well. Although a percentage estimate of the "number of growers" nationwide who use DDVP on mushrooms was supplied in the Faulkner/Sutherland note dated 11/2/94, BEAD was unable to supply a "percent of crop treated" estimate. It was agreed that DRES would assume 1% of mushrooms are treated with DDVP, since soil treatment before planting has become the primary means of insect control for this crop (personal communication, D. Sutherland, 11/7/94).

The PCT estimates supplied for dairy cattle and laying hens in the 10/26/94 memorandum were used in the DRES analysis, despite an additional effort of refinement (described in Faulkner/Sutherland note to Schaible dated 11/2/94) based on the length of the fly season north and south of the Mason Dixon Line and the percentage of dairy cattle and laying hens raised in each respective region. DRES acknowledges that there is probable overestimation of exposure and risk from milk and eggs due to the assumption that dairy cattle and laying hens are treated with DDVP all year long instead of only during the fly season. The percent crop treated estimate for beef cattle was applied only to beef cattle in the DRES analysis; the estimate for "other animals and other poultry" was assumed for hogs, goats, sheep, chicken, turkey, and other poultry.

While previous analyses have assumed a PCT estimate of 7.5%

(derived from data relating only to food processing plants) to apply to **all** raw and processed non-perishable bagged or packaged foods, **the present analysis assumes that percent of sites treated at various point in the distribution and processing channels should be added rather than averaged** (Faulkner/Sutherland, 10/26/94). In other words, the 20% estimate recommended by BEAD roughly reflects the sum of the PCT estimates for bulk storage, processing plants, and warehouses. In that food may not be treated with DDVP at all three sites, this assumption may lead to overestimation of exposure and risk.

b. **Naled:** It was assumed that less than one percent of any given crop would have residues of DDVP on it due to the use of naled to control mosquitoes and flies. For certain crops which are grown in with water-filled areas (e.g., sugarcane) this may be an underestimate. However, across all crops it is considered that this is a overestimate of percent of agricultural crops treated through this use.

In the absence of a clear definition by BEAD of cole crops, the percent crop treated estimate for "cole crops" was assumed for the DRES items "mustard greens", "kale", "kohlrabi", and "swiss chard"; where PCT information was given for a specific RAC belonging to the cole crop group, the RAC specific estimate was used instead of the "cole crop" estimate.

Anticipated residues

a. **Chronic analysis:** Anticipated residues (ARs) for use in the DRES chronic analyses were supplied by CBRS in a S. Hummel memorandum to D. Utterback and B. Lowery dated 9/12/94. Residues were supplied for dichlorvos from DDVP itself, dichlorvos from naled and dichlorvos combined from both sources. The combined residues were not used by DRES. ARs reflect field trial data and in some cases are further refined by processing factors (almost always reflecting cooking).

Reduction factors applied to DDVP-derived residues were calculated by looking at the degree of degradation of residues, the temperature at which foods were cooked, and the duration of cooking from several studies. These cooking factors ranged from 0.001 to 0.92. Naled-derived DDVP residues were refined by assuming a default 90% reduction of residues (or a cooking factor of 0.1) for cooked forms of RACs.

Because the residues supplied by CBRS were not consistent between DDVP and naled in their application of cooking factors, inconsistency exists between DDVP-derived risk and naled-derived risk. The use of cooking factors is consistent between the chronic and acute analyses for each source (DDVP, naled).

For both DDVP and naled-derived DDVP, cooked food forms of RACs existed in the DRES file for which only "raw" ARs were supplied in Hummel's 9/12/94 memo. In these cases, DRES adjusted the ARs supplied by CBRS to reflect cooking by multiplying the AR for the raw form by the default concentration factor of 0.1 which was used by CBRS in calculating cooked ARs for naled-derived DDVP. CBRS has agreed that this reduction of the ARs which were supplied is appropriate where the DRES food form of a RAC was cooked and the AR has not already been adjusted (personal communication w/ S. Hummel, 11/8/94).

Chemical specific assumptions in creating the anticipated residue file are discussed below. A summary of the residue and percent of crop treated information used in the DRES chronic analyses for DDVP and naled-derived DDVP are attached as Attachments 1A and 1B, respectively.

i. **DDVP residues-** Commodity specific assumptions made in generating and using "raw" and "cooked" ARs are included in Appendix A.

Because the nature of the tolerances which exist for DDVP (treatment with DDVP could occur during or after processing), underestimation of exposure could occur through the inappropriate use of processing factors to reflect reduction through processing when in fact residues are introduced to the food after processing. There are only a few commodities in the file for which this might be a relevant concern.

ii. **Naled-derived DDVP-** The use of the default reduction factor instead of more recently calculated cooking factors results in the aforementioned inconsistencies between risk assessments for DDVP and naled. But by comparing the calculated reduction factors to the default factor of 0.1 ppm, it can generally be said that using the default factor in the naled analysis underestimates risk from meat, milk, poultry and eggs, coffee and tea and overestimates risk from dry beans, rice, oils, and chocolate. Because naled tolerances are specific to either agricultural uses or to the mosquito/fly control use and therefore cooking will always occur <u>after</u> introduction of residues, inappropriate use of cooking factors is not expected to present uncertainty in the analysis as it does for DDVP. Commodity specific assumptions made in creating the naled-derived DDVP file are included in Appendix A.

b. **Acute analysis:** No high end anticipated residues were supplied by CBRS as tolerance level residues are generally recommended by the Chemistry Branches as being appropriate for acute exposure assessment. Therefore tolerance level residues were assumed for the DRES acute exposure analysis, adjusted by DRES staff using CBRS supplied cooking factors where the DRES food form indicated that the RAC had been cooked. The same assumptions used in the chronic analyses in applying cooking factors were used in the acute analyses as well.

For the analysis assessing risk from naled-derived DDVP, naled tolerances were converted to DDVP equivalents by multiplying tolerance levels by a factor of 0.58 (supplied through personal communication with M. Beringer, 11/14/94), reflecting the ratio of DDVP's molecular weight (221) to that of naled (380); DDVP tolerances were assumed in the DDVP analysis. Commodity specific assumptions for each DDVP source described in Appendix A were used in the acute analysis as well as the chronic analysis.

3. Results

Chronic Risk

The DRES chronic exposure analysis used tolerance level residues and 100 percent crop treated to estimate the Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population and 22 population subgroups. Anticipated residues and refined percent crop treated information were used to calculate the Anticipated Residue Contribution (ARC) for those same population groups. The ARC is considered the more accurate estimate of dietary exposure. These exposure estimates were then compared to the RfD for DDVP to derive estimates of chronic dietary risk from DDVP and from naled-derived DDVP. Summaries of the TMRCs, the ARCs, and their representations as percentages of the RfD are attached as Attachments 2A (DDVP) and 2B (naled-derived DDVP).

The ARC from published uses of DDVP for the U.S. population is 0.000054 mg/kg bwt/day, which represents 11% of the RfD. The population subgroup most highly exposed, non-nursing infants less than one year old, has an ARC of 0.000143 mg/kg bwt/day, or 29% of the RfD.

The ARC for the U.S. population from DDVP-derived from published uses of naled is 0.000016 mg/kg bwt/day, or 3% of the RfD. The subgroup most highly exposed, non-nursing infants < 1 yr. old, has an ARC of 0.000057 mg/kg bwt/day, or 11% of the RfD.

Given the chronic risk estimates from this analysis, it appears that chronic dietary risk from DDVP and naled-derived DDVP for affects other than cancer is minimal.

Cancer risk

The upper bound excess lifetime cancer risks from DDVP and naled-derived DDVP were calculated for the overall U.S. population using the following relationship:

$$\text{Upper Bound Cancer Risk} = \text{Dietary Exposure} \times Q_1^*$$

An upper bound potency factor (Q_1^*) of 1.22×10^{-1} (mg/kg/day)$^{-1}$ and a 70 year lifetime exposure were assumed in this calculation. **Based on these assumptions, the upper bound cancer risk from DDVP was calculated to be 6.6×10^{-6} and that from naled-derived DDVP to be 1.9×10^{-6}.** The cancer risk from DDVP alone exceeds the level that the Agency generally considers as posing a negligible risk; the risk from naled-derived DDVP falls within the range that the Agency considers as being negligible.

Cancer risks for DDVP broken out by tolerance expression (where able) are listed in Table 1 on the next page. Because the tolerance expressions relating to bagged and packaged non-perishable foods have not all been defined in terms of DRES commodities, it was not possible to break out cancer risk attributable to each tolerance at this time. A table listing individual cancer risks from DDVP for each commodity is attached as Attachment 3A.

Table 1: Upper Bound Estimates of Cancer Risk from DDVP

Tolerance Expression	Upper Bound Cancer Risk
Agricultural uses - lettuce - cucumbers - tomatoes - mushrooms - radishes	2.1 E-7 1.6 E-7 2.6 E-8 1.4 E-8 2.6 E-9 9.8 E-10
Milk	2.6 E-6
Eggs	2.1 E-7
Red meat	1.1 E-7
Poultry	3.7 E-8
Packaged or bagged, non-perishable processed food and RACs (incl. bulk stored, regardless of fat content)	3.4 E-6
TOTAL	6.6 E-6

The cancer risk from processed foods can be described because a defined commodity data set has been established for this tolerance expression. The foods contributing to this risk are those listed in J. Kariya's 8/23/91 memo plus dates, figs, hops, herbs and spices (processed commodities added to the file as part of this analysis). **Cancer risk attributable to packaged or bagged, non-perishable processed foods is 3.3 x 10^{-6}**; commodities contributing the greatest amount of risk are cane sugar, beet sugar, coffee, tea, corn and wheat. It should be kept in mind that should the registration for use on processed foods be canceled and the tolerance revoked, some of these commodities (most notably cereal grains) could still contain residues from one or more of the remaining tolerances; thus the net reduction in risk from DDVP would not be 3.3 x 10^{-6}.

Cancer risks by commodity for naled are attached as Attachment 3B. Roughly 70% of the cancer risk for naled is attributable to milk (1.3×10^{-6}).

Acute risk

Two acute analyses were performed: one estimating the acute exposure from DDVP from its published tolerances, and the second estimating exposure from naled-derived DDVP. The DRES detailed acute analyses estimated the distribution of single-day exposure for **consumers only** in the overall U.S. population and certain subgroups. The analyses evaluated individual food consumption as reported by respondents in the USDA 1977-78 Nationwide Food Consumption Survey (NFCS), assuming uniform distribution of DDVP in the commodity supply. Because neurotoxicity is the effect at the endpoint being evaluated, exposure and risk were calculated for all of the standard DRES subgroups: U.S. population, Infants < 1yr., Children 1 through 6, Females 13+ yrs, and Males 13+ yrs.

The Margin of Exposure is a measure of how closely the calculated exposure comes to the NOEL (the highest dose at which no effects were observed in the laboratory test), and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). The Agency is not generally concerned with MOEs of 100 or greater when the NOEL is taken from an animal study.

For these analyses, MOEs were calculated using both high end exposure and mean exposure for all five of the standard subgroups. The distributions of exposures are attached as Attachments 4A (DDVP) and 4B (naled-derived DDVP); the high end and mean MOEs for each subgroup are included on the right margin of each printout, as well as being summarized in Tables 2 and 3 below.

Table 2: Margins of Exposure (high end, average) for DDVP-derived DDVP

DRES subgroup	High end (99th %ile)	Mean
U.S. population	83	465
Infants < 1 yr.	83	263
Children 1 through 6	63	258
Females 13+ yrs.	100	552
Males 13+ yrs.	100	558

As can be seen from Table 2 above, high end MOEs for the U.S. population, Infants < 1 yr. and Children 1 through 6 from DDVP-derived DDVP appear to be of concern, being below the level the Agency generally considers as negligible for acute risk.

Although ARs reflecting cooking were used in this analysis, tolerance level residues were assumed for the raw forms of foods considered in this analysis; the assumption that tolerance level residues might exist on multiple commodities all consumed in the same day is a possible source of overestimation in this analysis.

Less than one percent of the population for each subgroup in the table above are exposed to DDVP at levels which result in the calculated high end MOE. By looking at the distribution of exposures on Attachment 4A, it can be discerned that for all subgroups the 95th percentile exposed individual would have an MOE of greater than 100. Because the output of the DRES acute analysis does not specifically give the exposure of the 95th percentile exposed individual, the actual MOE cannot be discerned from this analysis.

Table 3: Margins of Exposure (high end, average) for Naled-derived DDVP

DRES subgroup	High end (99th %ile)	Mean
U.S. population	8.3	92
Infants < 1 yr.	3.3	64
Children 1 through 6	3.3	36
Females 13+ yrs.	12.5	116
Males 13+ yrs.	12.5	138

As can be seen in Table 3, high end MOEs from naled-derived DDVP are significantly below 100 for all subgroups. Mean MOEs are below 100 for the overall U.S. population, Infants < 1 yr. and Children aged 1 through 6 years. By looking at Attachment 4B, it can be seen that those 95th percentile exposed individuals would have MOEs well below 100 for all subgroups. The assumption that every raw food consumed by an individual in a single day would contain a tolerance level residue (or that every cooked food would contain one tenth the tolerance level residue) undoubtedly results in overestimation of risk in this analysis, especially when one considers that most of the DRES items evaluated in this analysis were present through a tolerance meant to account for incidental residues to agricultural crops through the use of naled as a mosquito and fly control. However, it is not possible from this analysis to characterize the degree of overestimation which occurs due to this assumption.

It is expected that the relative severity of risk from naled-derived DDVP will be addressed as part of the risk characterization of naled for the reregistration eligibility decision document which is scheduled to be completed in fiscal year 1995.

Addition of DDVP and naled-derived DDVP acute exposure and risk estimates from these analyses is inappropriate.

Attachments

cc: DRES, CBRS, Tox 1, Caswell # 328

Appendix A
Residue Assumptions for DDVP and Naled-derived DDVP Analyses

DDVP

* for "chocolate" and "cocoa butter", residues were measured in cocoa beans, which are cooked in making chocolate; the chronic AR supplied by CBRS was used, tolerance x 0.003 (reduction factor) was used in the acute analysis. If chocolate itself is treated as a bagged and packaged processed food, then these analyses underestimate risk in that raw chocolate would actually have residues above the reduced AR used in the analysis. This discussion also applies to the commodity "carob" as well.

* "peanuts, raw" in DRES is assumed to mean roasted peanuts; "cooked" ARs were assumed for both raw and cooked DRES food forms in both the acute and chronic analysis

* it was assumed for beet sugar and cane sugar that sugars had already been refined at the time of DDVP treatment, and therefore "raw" ARs should be applied to raw food forms, and "cooked" ARs to cooked food forms.

* "potatoes, dried- raw" food forms in DRES were assumed to be raw, dried potatoes, thus making back calculation from the chronic AR supplied in Hummel's memo necessary since it assumed "dried potatoes" were cooked

* "raw" forms for meats in DRES were assumed to be raw; "unspecified" food forms were assumed to have been cooked

* the following commodities were assumed to be cooked <u>after</u> treatment with DDVP; ARs reflecting cooking were applied to raw, cooked, and unspecified forms of these RACs:

hops	coffee
tea	dry beans/peas
popcorn	soybeans
cereal grain	

  consumption of food items treated <u>after</u> cooking (e.g., cereals) cannot be broken out from consumption of the RAC itself (e.g., corn or rice); because these RACs were assumed to be cooked after treatment, this analysis is likely to underestimate risk for those food items where cooking did not occur after treatment.

* only those "oil" ARs supplied in Hummel's memo (peanut, corn, and soybean) were adjusted to reflect cooking

* DRES default concentration factors were turned off where ARs were supplied for a processed form

Naled

* the "melons" AR supplied in the CBRS memo was applied to "casabas" in the DRES analysis instead of the AR given for the miscellaneous category (of which casabas is a specifically mentioned commodity); the AR for melons was also assumed for "towelgourd" and "bitter melon"

* an AR for "citrus, peel" of 0.02 ppm was verbally communicated to S. Schaible by S. Hummel on 11/8/94; no AR for "peel" was supplied in the the 9/12/94 memo.

* as was done with the DDVP, the supplied AR for "potatoes, dried" was divided by 0.1 to back-calculate to the raw AR for the raw food form entry in the DRES file.

* DRES default concentration factors were turned off only where ARs were specifically supplied for a processed form

* the same assumptions that were made in the DDVP analysis for raw, cooked, and unspecified forms of meat, cereal grains, soybeans, dried beans, corn, peanuts, popcorn, and cocoa beans/carob were made in the Naled analysis as well

* unlike in the DDVP analysis, sugars were assumed to be refined <u>after</u> treatment with naled; therefore ARs reflecting cooking were applied to both raw and cooked forms of beet and cane sugar.

* "beans, succulent-unspecified" were assumed to be raw