4-29-83

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

MEMORANDUM APR 29 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor (25)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: William Burnam, Acting Chief
Toxicology Branch/HED (TS-769)

SUBJECT: Bladex; EPA Reg.#201-279 and 201-281. A New Teratology Study in Rabbit; PP#9F2232; Petition proposing a tolerance of 0.1 ppm in/on Soybean CASWELL#188C

Recommendations:

1. Relative to the teratogenic potential of Bladex, the requested action is not toxicologically supported until issues associated with the rat teratology study are resolved (see W. Dykstra review of January 26, 1983).

2. The submitted rabbit teratology study is classified as Core Minimum. However historical data are requested in order to more adequately evaluate the fetal findings reported in this study.

3. At the highest dose tested, 4 mg/kg/day (days 6-18 p.c.), some increase in anomalies was noted, apparently associated with significant maternal toxicity, and hence are not considered a true teratogenic response. The NOEL for maternal and fetal toxicity in this study is 1 mg/kg/day, and the LEL is 2 mg/kg/day.

REVIEW:

A Teratology Study in New Zealand White Rabbits Given Bladex® Orally. A study performed by Shell Toxicology Laboratory (Tunstall), Sittingbourne Research Center, England; Project #221/81, Experiment #AHB-2321; November 1982. Submitted on February 1, 1983 as document SBGR.82.357 by Shell Oil Company, Washington, D.C. 20036. Accession #071382.

Test Article: Bladex technical, 98% a.i. (SD15418) was supplied by Shell Development Company U.S.A. The positive control test material, Thalidomide (99% a.i.) was supplied by Gruenthal GmbH, West Germary.

Virgin female New Zealand white rabbits, 3-4 months old, were received in batches from Shell Toxicology Laboratory (Tunstall) Breeding Colony. The rabbits were then individually housed in three rooms and maintained at 16-20°C temperature, 43-74% relative humidity, and a 12-hour light/dark cycle. Food and water were available ad libitum. All animals were already eartagged for identification when 8 weeks old.

At mating, the animals were 7 to 11 months old and weighed 3.5 to 5.1 kg. Proven males from the breeding colony were used, and the day of mating was designated day 0 postcoitum (p.c.).

The animals used in this study were divided in 11 blocks (A-K) of 10 females each. One block was mated on each of the following days: 1st-3rd, 7th-10th and 14th-17th of June, 1982. After mating (on the same day) the females received 25 i.u. luteinising hormone intravenously.

Dosages of Bladex were then administered orally in gelatin capsules according to the following schedule:

Group	Dosages* mg/kg b.w./day	# of Capsules per day	# of Mated Females
1	0.0 Bladex	1 gelatin (days 6 to 18 p.c.)	22
2	1.0 Bladex	1 (days 6 to 18 p.c.)	22
3	2.0 Bladex	1 (days 6 to 18 p.c.)	22
4	4.0 Bladex	1 (days 6 to 18 p.c.)	22
5	150.0 Thalidomide	3 (days 7 to 10 p.c.)	22

*The control animals were given empty gelatin capsules instead of the Bladex capsules, and the positive control group was given thalidomide capsules. The dosages were within ± 2.5% of the nominal values; and were calculated based on day 0 body weights for days 6, 7 and 8 dosages, and based on day 6 body weight for days 9-18 dosages.

The animals were monitored daily for general health. The body weights were recorded on days 0, 6, 9, 12, 15, 18 and 29 p.c. Individual food consumptions were recorded over the periods 0-6, 6-12, 12-18, 18-24 and 24-29 days p.c.

All animals were sacrificed on day 29 p.c. by intravenous injection of sodium pentobarbital and necropsied. The intact uteri were removed, weighed (after the ovaries had been excised) and examined for the following parameters:

1. Number of corpora lutea.
2. Number of implantation sites.
3. Number of resorptions.
4. Number of viable and dead fetuses.
5. Weight and sex of each fetus.
6. Fetal abnormalities/anomalies (external, visceral or skeletal).

When an external abnormality was observed, the fetus was processed by the particular method for that particular abnormality. In the absence of external abnormalities, one third of each litter was randomly chosen to be fixed in Bouin's fluid, and the cranium of each fetus was sectioned for examination. The remaining parts of these fetuses were dissected and some individual viscera were sectioned and examined for abnormalities (Wilson, 1965). The remainder of the fetuses (approximately 2/3) were examined for visceral abnormalities then eviscerated, cleared and stained with alizarin-red for skeletal examination (Dawson, 1926).

Dead fetuses were also examined and all observed anomalies were reported. Fetuses of rabbits killed or found dead during the study and those of aborted rabbits were fixed in Bouin's fluid for visceral examinations.

Gross examinations were performed on all rabbits in this study at necropsy, and tissue samples of any observed lesion were fixed in 10% neutral formalin solution and processed for microscopic examinations.

Statistical Analysis:

The data were statistically analyzed using the two-sided tests throughout the study:

1. The analysis of covariance and the Dunnett's test (1964) were used for maternal and fetal weights and for food consumption.

2. The Wilcoxon's two-sample rank sum test with ties (Hill and Peto, 1971; Pearson and Hartley, 1972) was used to determine the significance of any difference between the vehicle control and treated groups for the number of live fetuses, corpora lutea, implantations, fetal losses, and the proportion of fetuses showing anomalies in the control and treated groups.

The comparisons between the control and treatment groups were made at the level of significance of $p<0.05$ and $p<0.01$.

RESULTS

Maternal Observations and Mortality:

No clinical symptoms were reported in this study except for a noted reduction in fecal elimination in the second half of the study period. This effect appeared to be dose-related at the mid and high dose levels and was also noted at the following rate: 3/22, 2/22, 9/22, 14/22 and 9/22 animals in the vehicle control; low, mid, high, and positive control groups respectively. This symptom was generally associated with extreme anorexia from day 18 to 29 p.c. in 1, 1, 4, 4 and 4 rabbits of the above affected animals in the control, low, mid, high and positive control groups respectively; and these animals were thin at necropsy and their stomachs were impacted with hair and feces. Also, increased number of animals in the mid, high and positive control groups reflected irritation and ulceration in the stomach mucosa and had intestines and stomach filled with gas and liquid. In addition, the average food consumption decreased in all treatment groups in a dose-response fashion during the compound administration period (see discussion on food consumption in the next section).

Few mortalities occurred in this study: One mid dose pregnant rabbit (#640) died on day 16 p.c., the cause of death was unknown; one high dose female, #717, was found moribund at the end of the study on day 29 p.c.; and one positive control animal, #454, showed signs of abortion on days 20 to 22 p.c. and was found moribound on day 28 p.c.

Abortions were reported in the treated groups as noted below: one mid-dose animal, #666, aborted on day 22 p.c.; two high-dose animals, #519 and 732, aborted on days 26 and 29 p.c. respectively; and two positive control animals #621 and #1606 aborted on days 27 and 29 p.c. respectively.

No mortalities or abortions were noted in the vehicle control or low-dose groups.

The following table reflects these data:

Dosages in mg/kg/day	Bladex 0.0	Bladex 1.0	Bladex 2.0	Bladex 4.0	Thalidomide 150
# of Pregnant Animals/ Initial # of mated animals	20/22	21/22	22/22	20/22	22/22
# of animals with abortion (day)	0	0	1(22)	2°(26,29)	2°°(27,29)
# of dead or moribund pregnant females (day)	0	0	1(16)	1°(29)	1(28)
# of animals with total resorption	1	1	0	1	1

°One high dose animal (#732) aborted on day 29 p.c.; all fetuses were dead; and another high dose animal (#717) was moribund at the end of the study; on day 29 p.c., all fetuses were dead. The registrant listed these animals among the female survivors when reporting the maternal cesarean data (see the cesarean data table, upper section, page 8 of this review).

°°One positive control animal (#1606) aborted on day 29 and some fetuses were alive in this litter; the registrant reported this animal among the female survivors with live litters (see cesarean data table, lower section, on page 8).

Postmortem examinations of all dams in this study did not reflect significant changes in the treated groups as compared to the control group. The main lesions noted were in the stomach (irritation, gas and liquid filled), kidneys (mild to moderate nephrosis in few animals) and heart (white plaques on aorta and foci of degeneration).

Body Weight:

The average maternal body weight decreased during the dosing period, days 6 to 18 p.c., in a dose-response fashion, i.e., the control group gained an average of 54 g as compared to an average weight loss of 7, 27 and 110 g in the low, mid and high dose groups respectively; the positive control group lost an average of 50 g during this period (although the Thalidomide administration was only performed on days 7-10 p.c.).

The table below reflects the mean maternal body changes during this study:

Maternal Mean Body Weight Changes (g)	Dosage (mg/kg/days 6-18 p.c.) 0 (Vehicle)	1.0	2.0	4.0	Thalidomide° (positive control
Day 0-6	16	43	55	29	27
6-9	48	-61	-28	-39	-30
9-12	3	5	-9	-7	6
12-18	3	49	10	-64	-26
18-29	46	18	-4	5	-18
6-18	54	-7	-27	-110	-50
6-29	100	11	-31	-105	-68
0-29	116	54	24	-76	-41
0-29 (adjusted)°°	-320	-381	-405	-435	-369

°Compound administered daily from day 7 to 10 p.c.
°°Adjusted weight: day 29 mean b.w. - uterus & content weight.

The loss of weight in the low-dose group appears to be biologically significant during the first three days of treatment, however due to the large body weight gain in this group for day 12 to 18 p.c. (49 g as compared to 3 g in the control group), the low-dose animals appeared to have partially recovered from the initial compound toxicity.

Food Consumption:

The decrease in the mean body weights discussed in the above section appeared to be coupled with a concurrent significant decrease ($p < 0.01$) in food consumption during the first week of dosing (days 6-12 p.c.) in the mid and high-dose groups and the positive control group. The high dose group continued to consume less food ($p < 0.01$) until the end of the dosing period. The decrease in food consumption was not significant in the mid dose during the second week of treatment (day 6-18 p.c.). The low dose group reflected a slight decrease in food consumption during the first week of treatment; however, this decrease was not statistically significant.

Cesarean Data:

The following table reflects the results of the uterine examinations as reported in table 4(a) page 19 of the submitted report:

"Table 4(a) - Litter data of rabbits surviving to day 29 of study

Number of Litters	BLADEX (mg/kg/body weight/day)				Thalidomide (mg/kg/day)
	Control	1.0	2.0	4.0	150
	20	21	20	19	20
Mean number of corpora lutea/dam	11.0	11.0	11.5	11.8	11.7
Mean number total implants/dam	8.1	8.0	8.5	8.3	8.7
Mean number resorptions/dam	0.8	0.6	1.2	1.6	2.7*
Mean number of dead fetuses/dam	0.2	0.3	0.4	1.5*	1.1*
Mean number of pre-implantation losses/dam	3.0	3.0	3.1	3.5	3.1
Mean number of post-implantation losses/dam	1.0	0.9	1.5	3.2**	3.8**
Number of litters[a]	19	20	20	16	19
Mean number of live fetuses/litter	7.5	7.5	7.0	6.1	5.2**
Mean number of live male fetuses/litter	3.6	3.8	3.5	2.8	3.0
Mean number of live female fetuses/litter	3.8	3.7	3.5	3.4	2.2*

*Significant difference from control ($p \leq 0.05$, Wilcoxon).
**Significant difference from control ($p \leq 0.01$, Wilcoxon)."
a: Number of litters with live fetuses at day 29 p.c.

Note: The mean weight of fetuses in grams was 42.5, 42.6, 40.5, 41.3 and 40.0 in the control, low, mid, high, and positive control groups respectively.

The table above indicated that no statistically significant effects appeared to be related to Bladex treatment except at the high dose level, as described below:

1. The mean number of dead fetuses/dam, 1.5, was statistically significantly ($p < 0.05$) higher than the control value, 0.2, and was also higher than the positive control value (1.1, $p < 0.05$). The mid dose value (0.4) and low dose value (0.3) were slightly higher than the control value but not significant.

2. The mean number of post-implantation losses/dam 3.2 was also significantly higher ($p < 0.01$) than the control value, 1.0, and within the same range of the positive control value (3.8, $p < 0.01$). The mid dose level reflected a moderate increase in this value (1.5) as compared to the control group, and the effect at this level appeared to be biologically significant. No effect was noted at the low dose level (0.9).

The mean number of resorptions/dam, was 0.8, 0.6, 1.2, 1.6 and 2.7 in the control group, low, mid and high dose Bladex group and positive control group respectively. A dose-response effect was noted at the mid dose level and above. However, this effect was only statistically significant ($p < 0.05$) in the positive control group.

A dose-response decrease was also noted at the mid dose level and above in the mean number of live fetuses/litter as compared to the control group, i.e., 7.5, 7.5, 7.0, 6.1, and 5.2 in the control, low, mid, high dose, and positive control groups respectively. This decrease was only statistically significant ($p < 0.01$) in the positive control group.

Bladex also appeared to slightly affect the male fetuses more than the females at the high dose level, i.e., the sex ratio was 2.8 males/3.4 females as compared to 3.6 males/3.8 females in the control group. In the positive control group, the number of females statistically decreased ($p < 0.05$) as compared to the control group and the sex ratio was 3.0 males/2.2 females. No effect was noted at the mid or low dose levels.

Finally, the mean fetal weight appeared to be slightly affected in the mid and high dose groups in this study.

Fetal abnormalities/anomalies

Major external anomalies were noted only in the high-dose group and included acephaly in one fetus, domed cranium in four fetuses from two litters and thoracoschisis in one fetus. Other minor anomalies were noted in the mid and high dose groups and included subcutaneous haemorrhage in one fetus in each of these 2 dose groups; and flexed carpals in one mid-dose fetus and four high-dose fetuses from two litters (this effect was also noted in one control fetus). No effects were noted in the low dose group.

Table #1 below summarizes the External Anomalies:

Dosage, mg/kg/day (day 6-18 p.c.)[a]	Bladex				Thalidomide
	0.0	1.0	2.0	4.0	150
Fetuses (litters) examined	142(19)	150(20)	139(20)	98(16)	98(19)
Acephaly °°	0	0	0	1(1)	2(2)
Domed cranium°°	0	0	0	4(2)	4(4)
Thoracochisis°°	0	0	0	1(1)	0
Subcutaneous haemorrhage°	0	0	1(1)	1(1)	1(1)
carpals flexed.°	1(1)	0	1(1)	4(2)	3(2)

°° Major malformations ° minor anomalies
[a] Thalidomide was administered on days 7 to 10 p.c.

It is noted that all the above findings in the high-dose group were limited to litters of two dams (#412 and #655) which reflected multiple anomalies in the same fetuses or in additional fetuses, see the 2 tables below on visceral and skeletal findings.

Table 2. Visceral Findings

(Note that one third of each litter was fixed in Bouin's solution and examined viscerally including transverse sections of the cranium. Data from these fetuses, and from some tissues of the remaining fetuses that were processed for skeletal observations, are listed below).

Dosage, mg/kg/day (days 6-18 p.c.)[a]	Bladex				Thalidomide
	0.0	1.0	2.0	4.0	150
Fetuses (litters) examined	47(19)	52(19)	45(19)	34(15)	33(19)
-Brain ventricles dilated[b]°°	1(1)	0	0	3(2)	15(9)
-Brain vestigial°°	0	0	0	1(1)	0
-Eye vestigial°°	0	0	0	1(1)	0
-Eye small and soft lens°°	0	0	0	1(1)	0
-Retina folded°°	0	1(1)	0	0	1(1)
-Thoracoschisis[c]°°	0	0	0	1(1)	0
-Azygos lung lobe absent°°	0	1(1)	0	0	9(7)

-kidney absent°°	0	0	1(1)	0	3(2)
-kidney pelvis dilated°°	0	0	2(1)	3(2)	0
-Ureter absent°°	0	0	1(1)	0	3(2)
-Urinary bladder dilated°	0	0	0	1(1)	0
-Gall bladder bipartite°	0	2(2)	2(2)	1(1)	7(6)
+**Gall bladder bipartite	2(2)	2(2)	4(4)	0	15(9)
-Gall bladder small°	1(1)	0	1(1)	3(2)	5(5)
+**Gall bladder small	1(1)	3(2)	3(3)	0	4(3)
+**Gall bladder hemorrhagic	0	0	4(3)	2(2)	5(3)
+**Gall bladder absent°°	1(1)	0	1(1)	0	0
-Heart rotated and atria dilated°°	0	0	0	1(1)	0
-Proximal portion of left° Common carotid and innominate arteries joined	1(1) 10(8)	3(3) 6(5)	4(3) 6(4)	2(2) 8(3)	1(1) 6(4)
-Testis undescended°	0	2(2)	0	0	1(1)
+** Ovary small°	0	0	1(1)	0	0

°°Major malformations ° minor anomalies/varitations

a: Thalidomide was administered on days 7 to 10 p.c.
b: Dilated brain ventricles were also reported in dead fetuses at the following incidence :0,0, 2 (2), 1 (1) and 7 (3) fetuses (litters) in the control, low, mid, high and postive control groups respectively.
c: This high dose fetus was previously reported under the external anomalies in table #1.
+** the effects reported under this sign represent additional data generated from the remainder of the fetuses (2/3 of each litter) which were processed for skeletal examinations. These fetal data will be added to the corresponding data noted above in the remaining one third of the fetuses, and compared to the historical control data when submitted.

Table #3. Skeletal Findings

Dosage, mg/kg/day[a] (days 6-18 pc.)[a]	Bladex				Thalidomide
	0.0	1.0	2.0	11.0	150
Fetuses (litters) examined	95(19)	98(20)	94(20)	64(16)	63(19)
-Cranium and hyoid bones					
Enlarged Fontanelle	9(3)	2(2)	7(3)	7(2)	9(7)
Sutural bone Present	3(2)	4(3)	3(3)	2(1)	3(3)
Delayed hyoid ossification	0	1(1)	0	0	0
Total	11(4)	7(6)	9(4)	9(3)	28(12)
-Vertebral abnormalities					
Caudal vertebrae reduced in numbers or absent.	3(3)	1(1)	7(2)[c]	1(1)	12(7)[c]

-Limb bone abnormalities

Forelimb digits delayed Ossification	4(3)	0	4(2)[d]	0	3(1)[d]
Hindlimb digits delayed Ossification	2(1)	0	1(1)	0	2(1)[d]
Tibial tarsal bones absent++	4(1)	0	7(3)[d]	2(2)	3(2)
-Sternebra abnormalities/anomalies[b]	43(18)	29(14)	43(18)	23(10)	39(17)
-Rib abnormalities (fused)	1(1)	1(1)	0	0	2(2)
-Rib variations (usually additional #13)	37(14)	47(17)	54(18)	43(14)	35(16)

a: Thalidomide was administered on days 7 to 10 p.c.

b: These sternebra abnormalities/anomalies included absent, small, or unossified sternebra #5 or other sternebra; and misalligned, misshapen, joined or forked sternebra.

c: The number of animals in the mid dose group was 91 and in the positive control it was, 61.

d: The number of animals in the mid dose group was 90 and in the positive control it was, 59.

The above tables summarize the abnormalities/anomalies noted in the Bladex treated groups and the corresponding findings in the positive control group. However, the anomalies which were noted only in the positive control group are not listed in the above tables because they are not needed in our comparison of the incidence rate of these findings with the Bladex effects.

The High Dose Group reflected the following major malformations:

1. Dam #412 had one fetus with acephaly and thoracoschisis; this fetus had also a vestigial brain and eye, and a rotated heart with dilated atria; three fetuses with domed cranium, two of which had dilated brain ventricles (one of these two had also carpal flexes) and the third had enlarged fontanelle; and three fetuses with flexed carpi, one of them was already described as having brain and cranium anomalies, another had dilated renal pelvis and the third had elongated fontanelles; an additional fetus in this litter had also enlarged fontanelle.

2. Dam #655 had one fetus with a domed cranium which also had dilated brain ventricles and renal pelvis; one fetus with flexed carpus and dilated renal pelvis; and a third fetus with small and soft eye lens.

3. Two additional high dose litters had skeletal cranium anomalies similar to those noted in the above two litters but no additional external or visceral cranium malformations were associated with these anomalies; dam #766 had two fetuses with the sutural bone present; and dam #766 had four fetuses with enlarged fontanelles.

We note that the above described cranium skeletal anomalies were noted in the control group, Bladex treated groups, and the positive control group. The incidence of these findings did not reflect a significant increase in the treated groups as compared to the control group. However, this reviewer cannot at the present time adequately assess the significance of these anomalies until historical data from the testing laboratory are available for review.

The submitted report stated on page 13 that "Apart from acephaly and thoracoschisis, which occur sporadically as background abnormalities, most of the abnormalities seen in these two litters (#412 and #655) were considered to be related to fetal immaturity due to the anorexia and body weight loss of the dams." This reviewer cannot at present agree with the above statement because no historical data were submitted from the testing facility. Hence, the backgound abnormalities cannot be adequately assessed.

In the mid dose group, one fetus had an absent kidney and ureter; another fetus in the same litter had an absent gall bladder (however, one control fetus had the same anomaly); two fetuses in a different litter had dilated renal pelvis; and one fetus had small ovaries.

In the low dose group, one fetus had a missing azygos lung lobe and another had a delayed hyoid ossification (these findings were not noted in the control or other Bladex groups); one fetus had two joined ribs (one control fetus had a similar rib anomaly); two fetuses from two litters had undescended testis, however this anomaly was not noted in the mid or high dose groups); and one fetus had a folded retina (a similar finding was noted in one positive control fetus; however, this finding was reported to be due to fixation and therefore may be an artifact.

Abnormalities/anomalies that were also noted in the Bladex treated groups at a slighly higher incidence rate than in the control group are the following:

1. Gall bladder abnormalities (small, bipartite, hemmorrhagic), i.e., hemmorrhagic bladder was noted only in the mid and high dose groups; small bladder was noted at a slightly higher rate in all Bladex treated groups; and bipartite bladder was noted in a dose-response fashion in the low and mid dose groups only (the incidence in the high dose group was lower than the control group.

2. The incidence of dilated renal pelvis was noted only in the mid and high dose groups.

3. Increased incidence of limb bone abnormalities (especially the absence of the tibial tarsal bones) was noted at a slightly higher rate in the litters of the mid and high dose groups as compared to the control group; but no effect was reported at the low dose level.

4. The percentage of fetuses (and litters) with more than 12 pairs of ribs slightly increased in a dose-response relationship in the Bladex treated groups as compared to the control group, i.e., 38(74), 48(85), 56(90), and 69(88) in the control, low, mid and high dose groups, respectively.

Other abnormalities (variations) were noted in this study; however, they occurred with similar frequencies in the control and Bladex treated groups, i.e., variations in branching of the common carotid and innominate arteries, sternebral anomalies and delayed ossification of the caudal vertebrae and of some limb bones. However, unless historical data from the testing facility are available for review, it cannot be determined at present if these findings are significant or reflect the background incidence level in this strain.

Conclusions

1. At the highest dose tested, 4 mg/kg/day, some increase in anomalies was noted, apparently associated with significant maternal toxicity, i.e. severe anorexia and weight loss, and hence are not considered a true teratogenic response. These anomalies are as follows:

Domed cranium in four fetuses of two litters and dilated brain ventricles in two of these four fetuses (an additional fetus with acephaly and multiple anomalies was also reported and belongs to one of these two litters). Dilated brain ventricles were also reported in 2(2) and 1(1) dead fetuses (litters) of the mid and high dose groups respectively.

Hence, this reviewer requests historical data to more adequately assess the findings in this study.

The positive control, administered 37 x the high Bladex dose (150 mg/kg/day for days 7-10 p.c., thalidomide), reflected some of the above findings, however at a much higher incidence rate.

2. Bladex is fetotoxic at 2 mg/kg/day and above. A dose-response increase was noted in the mean numbers of postimplantation losses and live fetuses per dam. A biologically significant increase was also noted in the array of skeletal variations noted at this dose level and above (i.e., absence of tibial tarsal bones and presence of additional rib #13).

3. Bladex causes maternal toxicity at 2 mg/kg/day and above, i.e. anorexia, weight loss, maternal death and abortion.

The NOEL for fetotoxicity and maternal toxicity is 1 mg/kg/day (LDT) and the LEL is 2 mg/kg/day (days 6-18 p.c.).

Classification: Core Minimum Data.

Historical data should be available to more adequately assess the findings in this study.

Amal Mahfouz 4/25/83

Amal Mahfouz, Ph.D. 4/25/83
Review Section V
Toxicology Branch/HED (TS-769) 4/25/83

TS-769:th:TOX/HED:4-22-83:AMAhfouz:card 6