

Summary of Presentation
to Dioxin Task Force
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The purpose of my presentation was to review what is known about the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Slide 1) to experimental animals and man. In regulating human exposure to TCDD, we are fortunate to have considerable information about the toxicity of this compound to humans. Information on human toxicity is generally not available on other compounds of environmental concern. However, in spite of the existence of a substantial data base, there are aspects of TCDD toxicity about which there is still considerable question. I will attempt to address some remarks to these data gaps.

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In my presentation I will confine my remarks to those toxic effects in experimental animals and man which are supported by objective and scientifically sound data. As is generally the case with environmental contamination with toxic compounds, there have been numerous "scientific" opinions for the existence or absence of toxic effects as a result of exposure of experimental animals or man to TCDD which are not consistent with the existing scientific data. I believe it is essential that we differentiate between those concerns or lack of concern for human health or environmental degradation which are based on scientific fact from those

based on speculation. With these distinctions in mind groups such as yours will be in a better position to make informed decisions concerning risks or potential risks resulting from human exposure to these compounds.

There have been a number of instances of human poisoning by TCDD. This slide (Slide 2) lists some of the more important ones. First of all there have been a number of accidents in industrial facilities which resulted in exposure of workers to TCDD. Most of these accidents have occurred during the synthesis of 2,4,5-trichlorophenol by alkaline hydrolysis of 2,4,5,6-tetrachlorobenzene. On July 10, 1976, an accident occurred in Seveso, Italy, which resulted in the exposure of a substantial nonindustrial population to TCDD. The importance of this particular accident is that it resulted in the first substantial exposure of women, particularly pregnant women, and children to TCDD under conditions in which unequivocal illness occurred. One minor incident resulted in the poisoning of two, or perhaps three, chemists involved in the synthesis of TCDD. The other major incident listed was the poisoning which occurred when used oil, contaminated with TCDD, was used for dust suppression on horse show rings in Missouri, an incident with which you are very familiar.

The acute toxicity of TCDD is quite variable depending on the animal species examined (Slide 3). The guinea pig is the most sensitive and the hamster the least sensitive of all the animal species that have so far been examined in detail. The acute toxicity in guinea pigs as compared to hamsters differs by approximately 5000-fold depending on the route of administration. It is frequently stated that TCDD is the most toxic

chemical known. This is, of course, not true. Botulinum toxin and tetanus toxin are more toxic than TCDD in all species examined. Also, in some species (e.g. the hamster), there are a number of compounds, including some insecticides in commercial use, which are more acutely toxic than TCDD.

What is the acute toxicity of TCDD in humans? In spite of a number of incidents of human poisoning, there is no evidence that a human fatality has occurred solely as a result of exposure to TCDD. However, in all of these incidents of accidental exposure, we have no definitive data on the doses to which humans were exposed. The only reasonably accurate dose-response data for TCDD toxicity in humans comes from studies carried out in Halmesburg Prison in Pennsylvania in the mid-1960's. In these studies, Dr. Albert Kligman of the University of Pennsylvania exposed approximately 60 prisoners to dermal doses of 0.2 to 16 μg of TCDD. These doses were reported to have caused no toxic effects. Subsequently, a similar number of prisoners (approximately 10) were exposed to larger doses, some as high as 7500 μg applied dermally in smaller doses over a period of a few weeks. These doses were reported to cause chloracne. However, no other clinical symptoms were observed in the subjects of these studies. When one considers all of these data, it is reasonable to conclude that humans appear to be one of the less sensitive species to the acute and subacute toxic effects to TCDD.

A number of studies have been performed examining the potential for TCDD to cause reproductive toxicity in experimental animals. This slide (Slide 4) shows the minimum dose of TCDD causing reproductive toxicity in

various species and in various studies. The data shown here for monkeys ignores the data generated in studies at the University of Wisconsin. There is considerable controversy surrounding the conduct of these studies. In my opinion, we must await replication of these studies by another laboratory.

It is important to note that the exposure of male mice (but not females) to high levels of TCDD for extended periods of time does not result in a decrease in reproductive capacity in that sex of that species. These data suggest that TCDD may exert its reproductive toxicity primarily in females. It will be important to examine males of other species to verify that this is the case.

There was no evidence of a statistically significant decrease in reproductive efficiency in the populations of women exposed to TCDD in the Seveso incident. I would again like to point to the particular value to toxicology of the data from Seveso. This unfortunate occurrence allows us to assess, although in a limited way, the potential for TCDD to cause reproductive toxicity in human females.

TCDD causes teratogenic effects in mice (Slide 5). The dose required is 1-3 $\mu\text{g/kg/day}$ administered during the 7-15th day gestation. Exposure of pregnant rats to certain doses of TCDD causes kidney anomalies in the offspring. There has been considerable debate whether this effect is a true teratogenic effect or, alternatively, the result of the acute toxicity of TCDD to the fetus. In my opinion, the data more strongly supports the

effect being the result of TCDD toxicity. To my knowledge no birth defects have been detected in monkeys born to or aborted from TCDD-treated mothers. Also, there was not a statistically significant increase in birth defects in the children born to or aborted from the pregnant women in Seveso who were exposed to TCDD. It was thought initially that an increase in birth defects may have occurred. However, a more careful examination of the data showed an obvious underreporting of birth defects in that region of Italy prior to the accident involving TCDD. When compared to a broader control base, there was not a statistically significant increase in birth defects observed in the exposed group in Seveso.

TCDD causes cancer in rats and mice (Slide 6). Tumors have been produced in mice whether the exposure is by way of the diet or applied to the shaved skin on the backs of the animals. The fibrosarcomas produced by dermal application of TCDD to mice is a particularly important observation when viewed in light of the suggestion that soft-tissue tumors may be increased in human populations exposed to TCDD.

A number of studies have been carried out looking for an increase in cancer and, in one study, mortality in humans who have been exposed or potentially exposed to TCDD (Slide 7). A study carried out in Sweden among forestry workers suggested a correlation between exposure to chlorophenols and chlorophenoxy acids and an increase in soft-tissue tumors. Subsequent studies in Finland among forestry workers and in New Zealand among agricultural workers (not shown) similarly exposed to chlorophenols and chlorophenoxy acids failed to show a similar correlation between exposure

and soft-tissue tumors. Workers exposed to chlorophenols and chlorophenoxy acids are also potentially exposed to various chlorinated dioxins and in some cases to TCDD.

There are a number of confounding factors in the Swedish study which prevent the examination of the existence or absence of a cause-effect relationship between TCDD exposure and soft-tissue tumors in humans. In the first place, the chlorophenols themselves may have been responsible for the increased incidence of cancer. The compound 2,4,6-trichlorophenol is an animal carcinogen. In addition, the forestry workers were also exposed to other commercial chemicals. These chemicals may have been responsible for the increase in soft-tissue tumors. Finally, an increase in soft-tissue tumors was also observed in forestry workers not known to be exposed to preparations containing TCDD. Thus, the correlation between TCDD exposure and an increase in soft-tissue tumors is questionable at this time. However, because of these human data and because dermal exposure of mice to TCDD causes soft-tissue tumors, further study of this issue is clearly warranted. These studies should be carried out in humans which have developed illness as a result of exposure to TCDD (See Slide 2).

An increase in gastrointestinal cancer has been observed in a population of workers poisoned by TCDD in an industrial accident. However, the fact that populations examined was small (about 50 subjects) and an increase in gastrointestinal tumors have not been detected in other TCDD-poisoned populations, raises doubts whether there is a cause-effect relationship between gastrointestinal cancer and TCDD exposure. Finally, a

population of U. S. workers (121 subjects) poisoned by TCDD in 1949 have been examined for an increase in mortality and various diseases (including cancer). No increases in mortality or morbidity, including incidence of cancer or death from cancer, was seen in this population.

TCDD can cause a number of toxic effects in experimental animals (Slide 8). In addition to acute lethality, reproductive toxicity and birth defects which have been discussed earlier, TCDD can cause liver damage in some species (rat, mouse), cause a decrease in immunocompetence (mice) and cause an induction of various enzymes in a number of species. The induction of enzymes is not known to have any clinical significance.

TCDD also causes a number of toxic effects in humans. These are shown in Slide 9. Of all the symptoms listed, the development of chloracne is the most frequent and sensitive response of humans to TCDD exposure. A careful examination of all the available data on human toxicity resulting from exposure to TCDD and the closely related compounds, the chlorinated dibenzofurans, strongly suggests that if chloracne is not present, the individual or individuals being examined have not been exposed to a sufficient dose of TCDD to cause other symptoms of toxicity. Often chloracne is the only symptom of TCDD toxicity seen in exposed humans. However, in the more severely exposed populations, liver damage and neurological effects are also seen. Other symptoms such as weight loss, hyperlipidemia, anorexia, hirsutism and loss of libido are also seen. Another reported manifestation of TCDD toxicity is porphyria cutanea tarda. However, because this condition is infrequently seen in humans poisoned by TCDD, it

is questionable whether porphyria cutanea tarda is caused by exposure to TCDD.

In summary, the acute toxicity of TCDD varies widely dependent on the species under examination. The current data indicate that man is one of the least sensitive species to the acute toxic effects of TCDD.

The most common and sensitive symptom of TCDD toxicity in humans is chloracne. In more severely poisoned subjects a number of other toxic effects are seen, the most important of which are liver damage and neurological effects.

TCDD causes cancer in rats when included in the diet and in mice when included in the diet or applied to the shaved backs of this species. The current data do not indicate there has been an increase in cancer in humans exposed to TCDD. However, there is a suggestion that there may be a correlation between soft-tissue tumors in humans and exposure to TCDD. Whether or not there is a cause-effect relationship between soft-tissue tumors and TCDD exposure will require additional studies.

1 DR. DONNELL: Our next speaker this afternoon will be
2 Dr. Robert Neal who is the President of the Chemical Industry
3 Institute of Toxicology in the Raleigh-Durham, North Carolina
4 area.

5 Dr. Neal is a biochemist, has been a professor,
6 teacher, researcher in the fields of biochemistry and
7 metabolism for a number of years before joining the Chemical
8 Institute. Some weeks back he came at the invitation of Mr.
9 Robert Feigenbaum to speak to the St. Louis area about the
10 dioxin.

11 It's a pleasure to have him back and to have him give
12 a more technical presentation this afternoon to the Task Force.
13 Dr. Neal.

14 DR. NEAL: Thank you very much. Perhaps, as Jay
15 Murray did, it might be useful to give a little background on
16 what my experience has been with dioxin.

17 CHAIRMAN JUDGE FINCH: Please do that.

18 DR. NEAL: There's been an area of research in my
19 laboratory for about ten years while I was at Vanderbilt up
20 until about three years ago when I moved to North Carolina.

21 It was an area of research, and out of that have come
22 a number of original contributions to the literature on the
23 metabolism and mechanisms of toxicity of TCDD.

24 Also involved in the Seveso incident invited over by
25 the Lombardi political, people in political power in the

1 Lombardi region soon after the Seveso incident to consult on
2 that and then was a member of a joint Italian U.S. committee
3 made up of our respective National Academy of Sciences that
4 dealt with this Seveso dioxin issue over a number of years.
5 That committee has since been disbanded but was in existence
6 for about four years.

7 Involved on an advisory panel of the Environmental
8 Protection Agency on what risk was inherent in use of 2,4,5-T
9 contaminated with dioxin in range land and rice for control of
10 weeds on those crops. It is a use of 2,4,5-T that is still
11 registered and a use for which is currently existent.

12 And the job of our scientific advisory panel was to
13 look at the accepted use of 2,4,5-T contaminated with dioxin to
14 the level of 100 parts per billion to make a decision whether
15 there was any immediate or substantial hazard to human health
16 as a result of use of that product for control of mesquite on
17 range land and weeds in rice. So that I've had a fairly
18 substantial regulatory and research involvement with this
19 interesting compound.

20 So I think with that sort of background let me
21 proceed then to give some information about the animal and
22 human toxicity of TCDD. Most of what I intended to say has
23 been said already by two previous speakers.

24 So I'll only amplify those sections of my
25 presentation which I think may give a slightly different

1 perspective than was presented by the two previous presenters
2 and spend less time on repeating data that they have presented
3 themselves previously.

4 I think one of the fortunate aspects of TCDD is that
5 we do have a substantial amount of information about the human
6 toxicity of this compound. It is a luxury that's not usually
7 afforded us on other compounds of environmental interest with
8 which we have to deal.

9 There are, of course--although in Missouri it maybe
10 seems that dioxin is the environmental issue, there are a
11 number of other issues before the public about environmental
12 contamination with other compounds that have the potential for
13 toxic effect.

14 We do have the luxury with TCDD of having substantial
15 human toxicity information which we, of course, should use in
16 evaluating potential toxicity of TCDD in various situations.
17 We're often left with trying to extrapolate from animal data to
18 man in terms of estimating.

19 In this case, we can modify those data which we've
20 generated in experimental animals with data we have in man to
21 arrive, I think, at a more informed decision relative to the
22 potential for dioxin to cause a toxic effect in any particular
23 situation.

24 I think in my presentation I'd like to stick as close
25 to the scientific data base as I can. With this issue of TCDD

1 and the gross politicization of it, one hears claims for the
2 absence or existence of a hazard from exposure to TCDD that
3 really is not backed by a scientific data base. There are
4 excesses on both sides, people claiming risk when the
5 scientific data base does not support the fact that there's
6 risk, others claiming that there's not risk when the scientific
7 data base would suggest maybe there is some. So there are
8 excesses on both sides.

9 I think it's important for a group such as this that
10 the decisions based on the scientific data base be separated
11 from those which are based largely on speculation. I think
12 speculation is essential in this kind of an issue, but you
13 ought to have a clear knowledge that this is speculation and
14 this is science. I think if one makes that distinction between
15 speculation and decisions based on science in this issue it
16 would probably be easier to approach this very difficult task
17 that you have before you in trying to decide what to do with
18 this issue that faces the State of Missouri.

19 So I'll try to point out those areas in which there
20 is a scientific data base to support a particular point of view
21 and those where it's largely speculation. So with that sort of
22 preface, let's look at some slides.

23 The first slide you've seen a number of times today.
24 So we'll not dwell on it. Here is a listing of human poisoning
25 cases with TCDD, and you've seen these before, perhaps, in a

1 slightly different form. Let's spend just a little time on
2 them.

3 The dozen or so industrial accidents involving worker
4 exposure. Perhaps in excess of 600 were made ill by these
5 exposures, and that is a data base that is available to us.
6 The unfortunate part about it is in those accidents we didn't
7 really have a good measure of what the exposure level was,
8 although it's clear that in most of the cases where the
9 exposure took place as a result of an explosion of a reaction
10 vessel involved in the synthesis of 2,4,5 trichlorophenol,
11 which is most of these, that the TCDD residues in those
12 explosions probably approached 1,000 parts per million and
13 sometimes exceeded that so that there was a substantial TCDD
14 contamination existent within these factories as a result of
15 these accidents.

16 The Seveso, Italy occurrence May 10, 1976, it was an
17 event that is a particularly important one in the history of
18 human exposure to TCDD because it was the first incident in
19 which there was substantial exposure of women, particularly
20 pregnant women, and children to TCDD. Prior to that, it had
21 been mostly industrial worker populations predominantly if not
22 exclusively male.

23 This was an event which allowed us to in this
24 incident look at the potential for exposure to TCDD to cause
25 reproductive toxicity in females and to cause birth defects in

1 offspring of those females, and it also let us look at
2 sensitivity of children to dioxin exposure by the dermal root.

3 Another incident is chemists involved in the
4 synthesis of TCDD, a minor event, and we'll not spend any time
5 and, of course, the Missouri horse show ring incident you know
6 well.

7 A number of people have shown this slide before.
8 There's one amplification that I have added there at the last.
9 This is a listing of the acute single dose LD50 of TCDD in a
10 number of species, and they're listed there: guinea pig most
11 sensitive, hamster the least sensitive. So that when you hear
12 the statement that TCDD is the most toxic synthetic chemical we
13 know, you really have to say what species are you talking about
14 because there are a number of compounds more toxic to the
15 hamster than TCDD, a number of compounds more toxic to the
16 bullfrog than TCDD so that you have to ask what species are you
17 referring to when you make that statement.

18 So I think it doesn't detract from the fact that is
19 an enormously potent compound in some species, particularly
20 guinea pig, but I think one has to keep it all in perspective
21 in looking across a number of different species.

22 You see there at the last that I've got what is the
23 acute lethal dose of TCDD in humans and a question mark, but
24 parenthetically I've added in excess of 100 micrograms per
25 kilogram. That data is probably the only data that we have of

1 a dose response in humans, and it came from a series of studies
2 that were carried out in Honesburg Prison in Pennsylvania in
3 1964 to 1968 by Dr. Klegman (Phonetic) from the University of
4 Pennsylvania in which he exposed prisoners dermally to TCDD.

5 The initial purpose of the experiments was to find
6 out what dose of TCDD applied dermally would, in fact, cause
7 chloracne in those prisoners. Initial experiments dealt with
8 concentrations of .2 micrograms up to 16 micrograms total
9 applied to the skin in acetone. Those doses did not, in fact,
10 produce any chloracne in those prisoners.

11 Subsequent experiments about which the data is not as
12 complete extended the dose up to 7,500 micrograms to some
13 individuals again applied dermally to the skin. So that those
14 individuals got 7,500 micrograms applied over a two-week period
15 to the skin dissolved in acetone.

16 Contrary to what might have been stated today, TCDD
17 applied to the skin of animals in acetone is almost 100 percent
18 absorbed. So that the dose in some of those individuals was in
19 excess of 100 micrograms per kilogram and chloracne was
20 produced in those individuals, but Dr. Klegman's statement was
21 that there was no other evidence, no other clinical symptoms of
22 toxicity.

23 The subject remained well throughout the study so
24 that we have a case in which we've exposed humans to a dose of
25 about 100 micrograms per kilogram sort of in the dose that's

1 listed there for rabbit and dog but no clinical symptoms of
2 toxicity other than the chloracne.

3 These, of course, the other species there where the
4 dose was applied orally, in this case it was applied dermally,
5 but one common point of reference is TCDD applied to the rabbit
6 skin is about half as toxic if it is administered orally. So
7 you can sort of double those numbers if you wanted to estimate
8 what the toxicity might be applied as a pure compound dermally.
9 So that we do have some human data suggesting that humans may
10 be one of the species less susceptible to the acute lethal
11 effects of TCDD or, perhaps, even to the sub-acute toxic
12 effects of TCDD.

13 This, of course, does not say anything about human
14 susceptibility to the chronic effects of TCDD, although we do
15 have epidemiological studies which we'll talk about in just a
16 few minutes.

17 Looking at reproductive toxicity, I've listed here
18 that dose which is sort of the minimum dose which causes
19 reproductive toxicity across a number of species. Listed there
20 for the monkeys I have not listed the data that was generated
21 by Allan at Wisconsin. That data is subject to considerable
22 controversy in terms of the conduct of those studies and the
23 validity of them. I think the data can't be completely ignored
24 but I think should be accepted with considerable skepticism
25 until they are repeated by some laboratory.

1 But you can see that reproductive toxicity is seen in
2 monkeys in another study at .05 micrograms per kilogram per
3 day, a fairly sensitive species.

4 Reproductive toxicity also seen in rats at .01. No
5 effect level is .001. What's interesting here is that in that
6 third line we see mice males exposed to 2.4 micrograms per
7 kilogram per day during about a 70-day period looking for
8 ability to produce reproductive toxicity in male mice and it
9 was without effect. That is a fairly substantial dose. If
10 you'd increase that dose very much over the period in which
11 this was administered, we would like to have begun to have some
12 fairly severe toxic effects.

13 This is a so-called dominant lethal effect, and it
14 measures the ability of a compound to cause reproductive
15 toxicity in males, and you can see that, in fact, it had no
16 effect.

17 The data currently available suggests that TCDD does
18 have reproductive toxicity, but it may be that it only has
19 reproductive toxicity in the female of species and not the male.
20 This data suggests that. It certainly doesn't completely
21 support that point of view, but it is a hypothesis that
22 certainly needs further investigation.

23 As far as humans are concerned, there was no evidence
24 of reproductive toxicity in the Seveso accident. The New
25 Zealand study which Dr. Murray showed you this morning where

1 they looked at reproductive toxicity in workers exposed to TCDD
2 by virtue of being exposed to the phenoxy herbicides doesn't
3 indicate evidence of a toxic effect either.

4 There was a study out of Dow looking at reproductive
5 toxicity in workers exposed to phenoxy herbicide manufacture.
6 Again, no evidence of reproductive toxicity in those couples.
7 So that it is unclear at this time whether the levels of
8 exposure to TCDD that have occurred in humans has any effect on
9 reproductive toxicity.

10 Teratology, it is a fairly good compound at producing
11 birth defects in mice with a level of 1 to 3 micrograms per
12 kilogram per day during the seventh to the fifteenth day of
13 gestation, the critical period for birth defects in that
14 species, whereas in rats even higher doses don't cause birth
15 defects but it does cause toxicity in the fetuses manifested in
16 hydronephrosis, a defect in the kidney, not a real birth defect,
17 but more a toxic effect on rats.

18 In the monkeys, although one saw increased incidence
19 of spontaneous abortion at these levels, we did not see
20 evidence of any birth defects in those aborted fetuses. In the
21 Seveso incident, the only incident in which we have had
22 substantial exposure to pregnant women to TCDD, we did not see
23 evidence of teratology in those.

24 DR. POWELL: Are you saying there were no higher
25 incidences of birth defects in Seveso?

1 DR. NEAL: There's not a significant increase in
2 birth defects in the Seveso incident.

3 DR. POWELL: As of when? I mean, is this something
4 brand new?

5 DR. NEAL: This is starting--

6 DR. POWELL: Talking about with the 1978 incident.
7 Is this a conclusion that's been recently reached?

8 DR. NEAL: I think it's been consistent throughout
9 all of the teratology studies that have been done in Seveso.

10 Looking at the incidence of cancer in experimental
11 animals, here is a listing. I think you've seen these before.
12 I think the one addition to the data that was presented today
13 is that in the bottom line you see the exposure of Swiss mice
14 dermally to TCDD .005 micrograms three times a week for 99
15 weeks does produce an increased incidence of fibrosarcomas in
16 mice. This is a particularly important finding, I think,
17 vis-a-vis the suggestion that soft tissue tumors may be
18 associated with phenoxy herbicide exposure in worker
19 populations.

20 I think this is an important finding that lead some
21 additional credence to the fact that this issue of soft tissue
22 sarcomas in exposed human populations need to be evaluated in
23 greater detail.

24 These are some of the epidemiological studies that
25 have been done. Of course, the Swedish studies with the forest

workers are actually two studies with Hardell being the major author. They did see an increase of soft tissue sarcomas. They also in the second study some evidence of an increased incidence of malignant lymphoma in these populations, both Hodgkin's disease and non-Hodgkin's lymphoma.

A similar study in Finland which looked at a similar population as was examined in the Swedish study have not seen this increased incidence of soft tissue sarcomas or lymphoma, although the period from exposure to examination was less in the Finnish study than in the Swedish study.

Also, a recent study in New Zealand in which again workers exposed to phenoxy herbicides in its agricultural use did not show a relationship between that occupational exposure and soft tissue sarcomas.

Nevertheless, the result of the Swedish study and the fact that in two studies done in the United States there is evidence of soft tissue sarcomas which exceed that which was expected, individually each of these studies is not a significant finding. But when you combine those three findings together, it is suggestive that there may be a relationship and certainly needs to be explored.

I think the key thing is that in the Swedish studies these individuals were exposed to a large number of different compounds: the phenoxy herbicides, the chlorophenols, and other herbicides in addition to 2,4,5-T where they might have

1 been exposed to the TCDD.

2 In addition, there seemed to be a relationship
3 between soft tissue sarcomas and exposure to herbicides not
4 containing the 2,3,7,8 isomer. So that I think on balance one
5 cannot see a cause effect relationship between soft tissue
6 sarcomas and exposure to the TCDD itself, but the relationship
7 is sufficient that I think it certainly requires some
8 additional emphasis on the part of epidemiological studies
9 looking to either reinforce that relationship or indicate that,
10 perhaps, there is not a relationship.

11 In the study in Germany, there was an increased
12 incidence of gastrointestinal tumors, although the number of
13 individuals examined was about 50 and the statistical
14 significance of this is also open to some question I think
15 particularly since it's not seen in other epidemiological
16 studies of individuals who were, in fact, exposed to TCDD and
17 developed chloracne.

18 I think another issue relative to soft tissue
19 sarcomas is that in European populations of industrial workers
20 who developed chloracne as a result of exposure to TCDD there
21 didn't seem to be any relationship between that exposure and
22 soft tissue sarcomas as well.

23 The final study, the Nitro, West Virginia study, has
24 been discussed before. No significant increase in cancer
25 mortality. No significant increase in mortality overall, but

1 again, it was 121 individuals, a fairly small population.

2 One cannot draw definitive conclusions from that,
3 although I think you need to realize that from a study like
4 that you certainly get a perception of what the level of risk
5 below what the upper level of risk might be and so that these
6 kinds of studies although small do give you valuable
7 information and you have to realize that these people were
8 likely exposed to fairly heavy doses. So that I think one can--t
9 this information is valuable in making some overall assessment
10 of what risk might be to individuals exposed to low levels of
11 TCDD.

12 Here are some listing of other toxic effects in
13 experimental animals that we will not spend any time on except
14 that final one where TCDD does cause induction of a large
15 number of enzymes particularly in the rodent livers. To date
16 activities of a dozen enzymes are induced, but there seems to
17 be no clinical significance between that induction and the
18 toxic effects seem to be no connection between the induction
19 enzymes and any of the toxic effects that are seen. In other
20 words, stated more clearly, enzyme induction itself does not
21 cause any toxicity.

22 Other toxic effects seen in TCDD exposed humans are
23 listed here and other people have talked about them. One
24 effect that may not have been discussed in much detail was the
25 hypercholesterolemia and hyperlipidemia that has been seen

1 reasonably consistently in heavily exposed human populations.
2 The clinical implication of this is unclear, but nevertheless
3 it is seen as a fairly consistent effect of TCDD exposure where
4 the exposure has been fairly heavy.

5 You notice I have not included porphyria cutanea
6 tarda because I think there's reasonable data to suggest that
7 it may not be related to TCDD exposure. It has occurred in a
8 couple of cases, but its inconsistent appearance of it in human
9 populations even those that they are heavily to TCDD suggests
10 that in those few cases the porphyria may have resulted from
11 exposure to other compounds to which the workers were exposed
12 during that incident.

13 Some Canadian scientists have made a fairly detailed
14 review of the data of human and animal toxicity of TCDD in
15 documents that have been published recently also come to that
16 same conclusion that they question whether there's a
17 relationship between TCDD and porphyria cutanea tarda in man.

18 Here is again showing of that Poiger (Phonetic) and
19 Slater (Phonetic) data on dermal absorption of TCDD depending
20 upon the vehicle in which it's found.

21 One correction is that the measurement that they
22 performed is really the percent of the dose in the liver after
23 twenty-four hours rather than the percent absorbed as was
24 indicated earlier today.

25 I think one important point in trying to correlate

1 this data with dermal exposure in the Missouri situation is
2 that the soil, the exposure to soil in this case was as a soil
3 water paste which would maximize dermal contact between the
4 soil and the skin, and in a normal situation exposure to the
5 dirt would be in its granular form so that the surface contact
6 would be only a fraction of that which is depicted here. It
7 says that the percent absorbed would undoubtedly be much less
8 than even depicted here.

9 So that the effect of soil on absorption of TCDD
10 through the skin is, it's considerably attenuated by it being
11 observed onto soil.

12 I'm going to get through rather early here because
13 we're skipping over a lot of data that's been repeated. Let me
14 just then summarize.

15 Acute toxicity of TCDD varies widely in animals. The
16 evidence currently available suggests man may be one of the
17 less sensitive species to the acute and, perhaps, subacute
18 toxic effects of TCDD.

19 This does not say one cannot generalize from that
20 that they may also be less sensitive to the chronic toxicity
21 effects of TCDD although one looks at the epidemiological
22 studies that have been done in workers who were exposed to TCDD
23 to the point that they developed chloracne and other clinical
24 symptoms and it would suggest that man may also be reasonably
25 resistant to the chronic effects of TCDD particularly in those

1 studies where the time between exposure and examination has
2 been twenty to thirty years.

3 Common symptoms in humans are chloracne, and my
4 interpretation of the data is that if the root of exposure is
5 dermal you're not going to have any other symptoms of toxicity
6 of TCDD in the absence of chloracne. That's a matter of
7 interpreting that data; but as you look at the industrial
8 accidents that have occurred in the Seveso incident and look at
9 the percentage of people complaining about a particular toxic
10 effect of that exposure, without exception chloracne exceeds
11 the other symptoms by a substantial percentage so that my
12 feeling is that if the root of exposure is dermal as it is in
13 almost all of these cases the first symptom that is going to be
14 seen is chloracne and then in the absence of chloracne
15 individuals are not likely to be suffering from any other
16 symptom of TCDD toxicity. Other symptoms of TCDD toxicity are
17 shown here.

18 TCDD does produce cancer in mice and rats. No cause
19 effect relationship between TCDD exposure and cancer has yet
20 been shown in man; but because of that suggestion of a
21 relationship between exposure and soft tissue tumors, it
22 certainly needs to be investigated further.

23 As a number of individuals have indicated today, the
24 availability of TCDD for dermal absorption really varies with
25 the formulation. If it's in an easily evaporable solvent such

1 as acetone or methanol, the skin absorption is substantial,
2 perhaps as much as 100 percent of it. If it's in soil, the
3 absorption is considerably attenuated. Thank you.

4 CHAIRMAN JUDGE FINCH: Do some of the Task Force have
5 questions of Dr. Neal?

6 DR. ROUSH: What about half life?

7 DR. NEAL: Yes. The question was what about half
8 life. What is the half of TCDD in animal organisms. There's a
9 substantial data base on that. The species in which there is
10 the shortest half life is the hamster where the half life is
11 about eleven to fifteen days, in other words, half of a dose.
12 If you give a hamster a dose of TCDD, half of that dose has
13 been excreted in two weeks. Then the half that is remaining,
14 half of that is excreted in another two weeks. So that it
15 halves it every two weeks.

16 As you look at the guinea pig and the rat, the half
17 life is about thirty days so that half of a dose that you have
18 given to a rat or a guinea pig is gone and excreted in thirty
19 days and in thirty more days half of what's remaining is
20 excreted and it continues.

21 The cow has a half life of about 120 days. The
22 monkey a half life of about 70 days. The goat something like
23 100 days.

24 DR. ROUSH: And man?

25 DR. NEAL: So that one has to say where does man fit

1 into this. I think if you look at it in terms of man's size
2 relative to other animals there seems to be as you get larger
3 there is a longer half life. I would suggest, perhaps, man
4 does fit at the 100 day half life area.

5 I think the thing that supports perhaps that man does
6 have a fairly reasonable half life is that there have been a
7 number of occasions where there have been attempts to measure
8 TCDD levels in human tissues subsequent to an exposure to TCDD,
9 and all except one of these measurements have not revealed the
10 presence of TCDD in adipose tissue or plasma.

11 This one exception is a woman in Seveso who died some
12 seven months after the absence of a primary liver tumor. The
13 tumor existed before the exposure, but they detected TCDD in
14 the liver of that woman and that was an unequivocal analytical
15 finding.

16 But there have been a number of other attempts in
17 humans and without success in detecting the TCDD in the human
18 male plasma and tissues so that it would suggest that it has a
19 reasonable half life and is excreted and probably falls into
20 that range of 15 to 120 days that exists for other animal
21 species that have been examined.

22 DR. POWELL: I was wondering if you also feel as
23 someone else mentioned this morning that if you ingest dioxin
24 somehow this will also appear first, any symptoms will appear
25 first before chloracne?

1 DR. NEAL: Yes. The only human exposure situation
2 that we have where we can answer that with some reasonable
3 certainty is the Yusho incident in Japan. Now, this was not
4 TCDD. This is 2,3,7,8 tetrachlorodibenzofuran, but the
5 experimental data suggests that there is, I think,
6 unquestionably the mechanism by which the dibenzofuran,
7 tetrachlorodibenzofuran causes its toxicity is identical to the
8 mechanism by which TCDD causes its toxicity. And the toxicity
9 of the dibenzofuran is not greatly different in the guinea pig.
10 Dibenzofurans LD50 is 5 micrograms, an extraordinarily low or
11 extraordinarily high level of toxicity in extraordinarily low
12 dose to cause toxicity.

13 In that Yusho incident, we did, in fact, have
14 substantial ingestion of the dibenzofuran, and you look at the
15 complaints of symptoms in the Yusho patients. The symptom that
16 predominated was, in fact, chloracne.

17 My feeling is that, and I'll go back to animal data
18 now, in the rabbit you can produce chloracne by giving the
19 animal TCDD interperitoneally but the level required is higher
20 than if you apply it dermally to the ear itself.

21 But I still think that the predominant symptoms are
22 going to be chloracne, but I'll reserve the fact that there may,
23 in fact, be other symptoms of toxicity by oral ingestion. But
24 in a population group, the predominant symptoms that are going
25 to be seen is chloracne. I'll use that Yusho incident and the

1 incident in Taiwan which is just a repeat of the Yusho in a
2 substantial population 2,000 in Taiwan, something like 1,200 in
3 in the Yusho. So we have a fairly substantial human population
4 exposed orally to a compound which exerts as toxicity the same
5 way that TCDD chloracne is the major symptom.

6 DR. POWELL: Let me go back for a minute to this
7 question of problems with birth defects at Seveso. I'm looking
8 at some studies here that indicate--and they aren't saying this
9 is a conclusive study. This is 1980 or 1981, I guess. There
10 are increased incidences of birth defects, Down's Syndrome is
11 one that they--I mean, they aren't standing up and beating a
12 drum. They aren't saying it's absolutely the case. They're
13 more saying "Well, we've got something in one case. The factor
14 is a factor of 100 in cases of--and they say that it's just
15 something that has to be followed and they have to do further
16 base line studies.

17 Now, that's why I asked you was this a conclusion
18 that's recently been reached that you were saying?

19 DR. NEAL: No. At the beginning of my talk, I said
20 I'm going to only cite those biological effects for which
21 there's a scientific data base to support it. That incidence
22 of birth defects in the Seveso area, the exposed area versus
23 the control area in the Lombardi, there was not a statistically
24 significant increase.

25 It is partially a function of the small numbers that

1 were generated during that time, but the scientific--if you
2 look at this data scientifically, there is not a statistical
3 significant increase in birth defects in that population.

4 DR. POWELL: But we need a larger population.

5 DR. NEAL: But I think supporting that also is the
6 other studies that have been done of reproductive toxicity in
7 other populations.

8 The New Zealand study which is a fairly substantial
9 one would tend to support that point of view as well.

10 MR. FORRESTER: Has there been any reproductive
11 studies around the Yusho dibenzofuran incidents?

12 DR. NEAL: The only reproductive--there were some
13 increased incidents of spontaneous abortion in those people in
14 the Yusho incident. The data, I think, in the Taiwan incident
15 hasn't been--so that there was a significant increase in
16 incidence of spontaneous abortion in the Yusho incident,
17 significant increase in low for gestational weight babies.

18 In other words, the weight of the baby at birth was
19 less than it should be, but these were substantial exposures.
20 These people were quite ill. The babies had skin changes at
21 birth.

22 DR. MARIENFELD: How long ago did Klegman do his work?

23 DR. NEAL: 1964 to '67.

24 DR. MARIENFELD: Have those individuals been followed?

25 DR. NEAL: I think they're lost. They certainly

1 would be a great population to follow because here we have
2 really our only good data of dose response in humans, and it is
3 unfortunate that the initial population in the lower dose
4 studies was about 60.

5 The population in the higher dose studies was 10. So
6 that the ones which got the substantial doses of 7,500
7 micrograms were much smaller in number.

8 DR. MARIENFELD: Has any attempt been made to locate
9 them?

10 DR. NEAL: I don't have first-hand knowledge of that.
11 I would think there probably has not been. I think the legal
12 ramifications of a follow up of that population particularly
13 since the climate for use of prisoners in these kinds of study
14 has radically changed since that was a common practice would
15 suggest that probably no one is eager to pursue that.

16 CHAIRMAN JUDGE FINCH: Or even willing.

17 MR. DOUGLAS: We've talked about half life and that
18 subject. We often hear that it's bioaccumulative. What about
19 that?

20 DR. NEAL: No. It is excreted in both urine and
21 feces, and it is the metabolites that's excreted. That's been
22 a major area of research in my laboratory is examination of the
23 metabolism of this compound. It is metabolized at a reasonable
24 rate.

25 In other words, in the guinea pig if you give a dose

1 fifteen days later, half that dose is gone if it's all been
2 metabolized. And all animal species we've looked at so far do
3 metabolize it to products that are much less toxic than the
4 parent compound. So that some compounds that are metabolized
5 are metabolized to more toxic products, but in the case of TCDD
6 as far as the acute toxicity is measured--

7 MR. DOUGLAS: Where do these statements come from as
8 far as bioaccumulation of it?

9 DR. NEAL: They have no basis in experimental fact
10 because it is a compound with a relatively short half life if
11 you look at it relative to some of the chlorinated--
12 polychlorinated biphenols which have a very long half life or
13 aldrin or dieldrin or DDE, the metabolite DDT which have a very
14 long half life. TCDD does not have that. It's not
15 particularly bioaccumulative.

16 MR. DOUGLAS: That's a particular significant
17 observation to me, particularly when you have a population
18 exposed to normal levels whether or not it is bioaccumulative.
19 What you're saying is that you break it down.

20 DR. NEAL: Oh, yeah.

21 DR. STALLINGS: I'd like to offer a comment in
22 relationship to the aquatic furans. The relative incidence of
23 the dibenzofurans is about one-forty thousandth or one-one
24 hundred thousandth that of TCDD in the environment. I think
25 the point might be well clarified if you feed an animal that is

1 no longer exposed to this material, you will see a decline. If
2 the organism is continually exposed to environmental input, the
3 level will be maintained at a level greater than that that is
4 exposed in aquatic organisms.

5 So you might expand briefly on the difference in
6 terms of the environmental accumulation versus one dose
7 response.

8 DR. YOUNG: I'll address that for you, show you what
9 studies that we actually have in the environment.

10 CHAIRMAN JUDGE FINCH: Okay, fine. Any other
11 questions of the Task Force?

12 DR. ROUSH: What about the implication of it being
13 not mutagenic?

14 DR. NEAL: Yes. Well, it is a mixed bag of data.
15 Most of the in vitro methods for detecting ability of TCDD
16 cause permanent alteration of the DNA are negative, although
17 there's a recent study out of the Air Force at Wright Patterson
18 (Phonetic) that suggests that in a test of mutagenicity not
19 often used there is some suggestion that it is, but
20 measurements of covalent binding of TCDD to DNA in animals are
21 essentially negative. So that I think on balance the
22 suggestion is that it probably is not mutagenic in most systems
23 and may not be mutagenic in animal systems as well.

24 DR. ROUSH: What implications does that have?

25 DR. NEAL: It would suggest, in fact, that TCDD may

1 be causing an increase in tumors in experimental animals by a
2 promotional rather than by a mechanism causing irreversible
3 change in the DNA, in other words, an initiating mechanism.

4 Implications of that in terms of risk assessment,
5 though, I think are not--there's really not much of a way of
6 differentiating between a tumor caused by a promoter and a
7 tumor caused by initiator is still a tumor. And if it's a
8 malignant tumor, it's going to kill you.

9 I think the only factor that would ameliorate it is
10 that promoters have to be, you have to be exposed to a promoter
11 for a substantial period of time. A single dose does not
12 promote. It takes a substantial period of promotion before a
13 tumor then is self-sustaining. If you stop short of that, then
14 you have to start over at the beginning again.

15 I think a good contrast here is aflatoxin. Aflatoxin
16 is present in some of our foods at a level of 15 parts per
17 billion, and it's allowed in peanuts and corn at that level for
18 human consumption. It is a much more potent carcinogen than
19 TCDD. A single exposure to one microgram of aflatoxin will
20 cause hepatomas in a trout. It is an extremely potent
21 carcinogen. It is an initiator.

22 A single exposure will cause tumors. So that it is a
23 much more potent carcinogen than is TCDD, but it's an
24 unavoidable contaminant of our peanuts and our corn because the
25 mold grows on those products and it's just impossible to market

1 corn or peanuts without the aflatoxin being present. As far as
2 a carcinogenic risk, the aflatoxin likely poses a much more
3 substantial risk than does TCDD but an unavoidable one because
4 it is contaminating a food stuff which is part of our diet and
5 that which we can't avoid.

6 I think that needs to be kept in perspective that
7 TCDD likely doesn't cause tumors except over an extended period
8 of exposure because the data suggests is a promoter. Aflatoxin,
9 on the other hand, a single exposure to a reasonable dose may,
10 in fact, initiate that process that will eventually express
11 itself as a tumor.

12 CHAIRMAN JUDGE FINCH: Any other questions? Thank
13 you very much, Doctor. We appreciate your coming out.

14 Dr. Donnell.
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