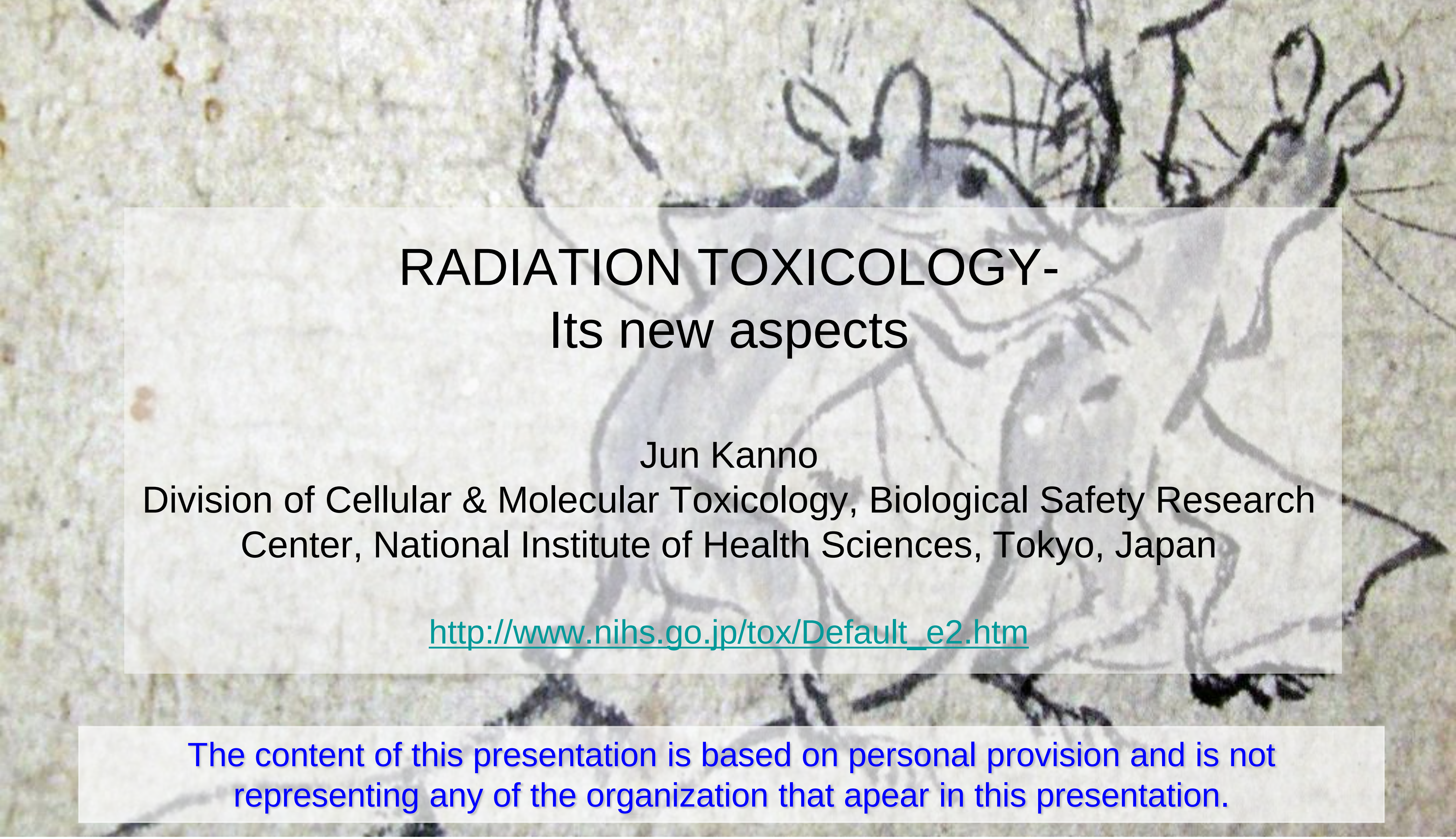


RADIATION TOXICOLOGY- Its new aspects

Jun Kanno
Division of Cellular & Molecular Toxicology, Biological Safety Research Center, National Institute of Health Sciences, Tokyo, Japan

http://www.nihs.go.jp/tox/Default_e2.htm

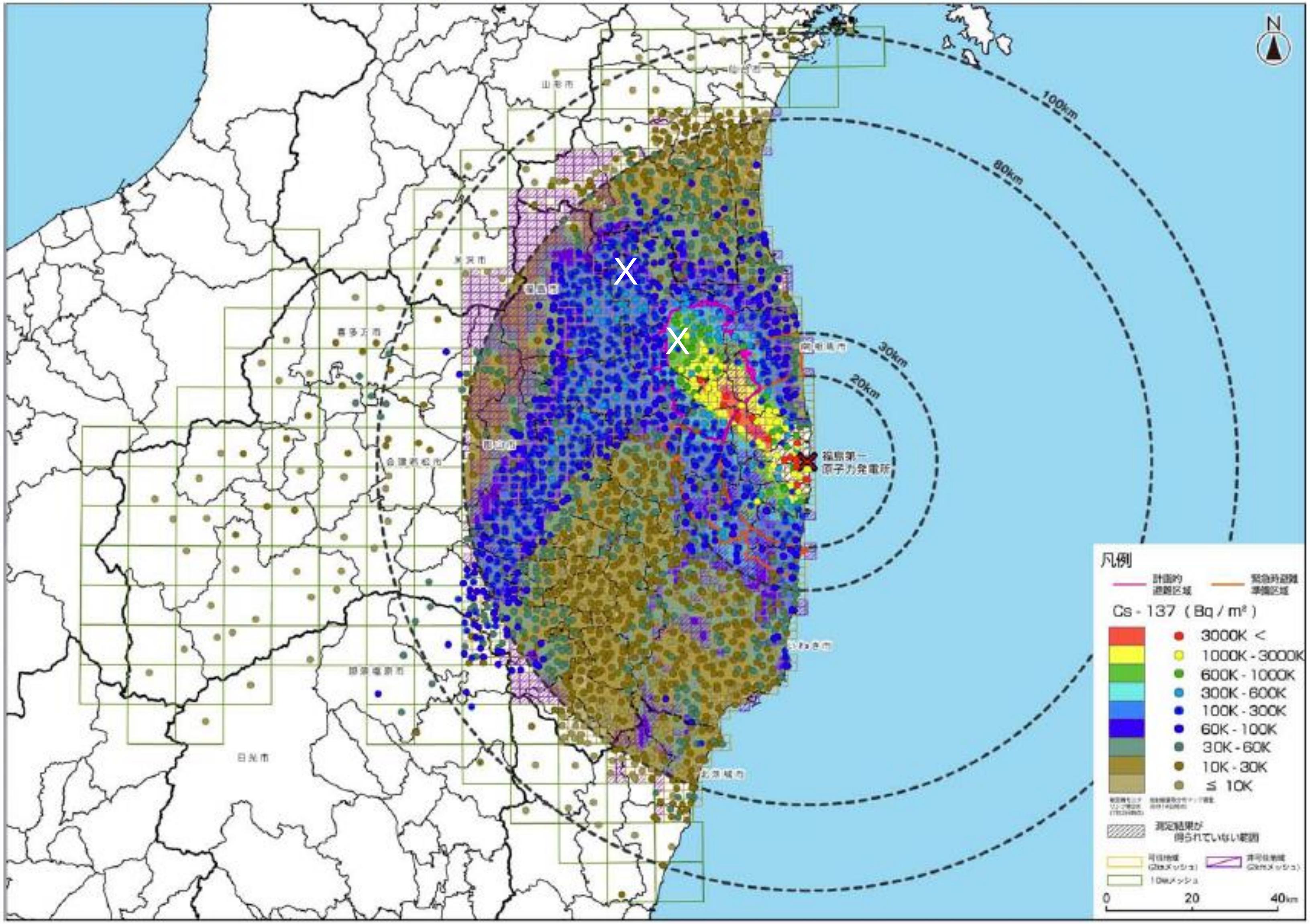
The content of this presentation is based on personal provision and is not representing any of the organization that apear in this presentation.

From 鳥獣人物戯画 Caricatures of Animals and Humans (12~13th Century) considered as the oldest cartoon in Japan)

2013-06-19 40th JSOT @ Makuhari

第3次航空機モニタリング結果とセシウム137の土壌濃度マップの比較について

別紙６



VSD (virtually safe dose)

Chemicals

- 10^{-6}
- 10^{-5}

- 10^{-4}～ 10^{-3} Asbestos (occupational)
  - In Japan, mesothelioma patient is 1,000 per year, with unknown numbers of lung cancer.

Radiation

- 10^{-2} 100mSv (threshold anounced by Japanese FSC*)

if dose rate effect is considered,

DDREF 100mSv = 10^{-4} ?

FSC: Food Safety Commission of Japan

“Magical effect” of Radiation

- Rheumatoid arthritis
  - Anticancer drug “methotrexate” is effective.
  - Radiation is also reported to be effective

In case of radiation, some one says “ therefore low dose radiation is good for health”, and mass media picks it up for news.

●However, nobody will say that “anticancer drug methotrexate is good for your health”, and no mass media will pick it up.

Practical Problems in Fukushima

- First problem:

“Mund therapie” by a certain radiation experts given to the exposed population “There is no scientific evidence that the cancer are clearly induced below the level of 100mSv, and hence, no need to fear”. “Stress will be more harmful, so do not seriously consider a small amount of radiation”.

(Which is perfectly adequate for those who were exposed)

was also announced to the non-exposed people, and people who might get exposed in the near future.

Practical Problems in Fukushima

- Second problem:

Food Safety Committee of Japan had set a threshold of 100mSv / whole life.

This made those who wanted to work at places above that level difficult to do so, and those who wanted to avoid as much as possible difficult to evacuate.

= narrowed the choice of people having different idea.

Practical Problems in Fukushima

- Unrealized problem:

Failed to arrange “Round Table Discussion” among all stakeholders.

This failure slowed down the decision making of the government (Capital and Local).

Aflatoxin (human exposure)

- **High dose exposure**
  - 2004 Kenya — 317 exposed, 125 dead
  - 1974 India — 397 exposed, 106 dead

Similar to radiation

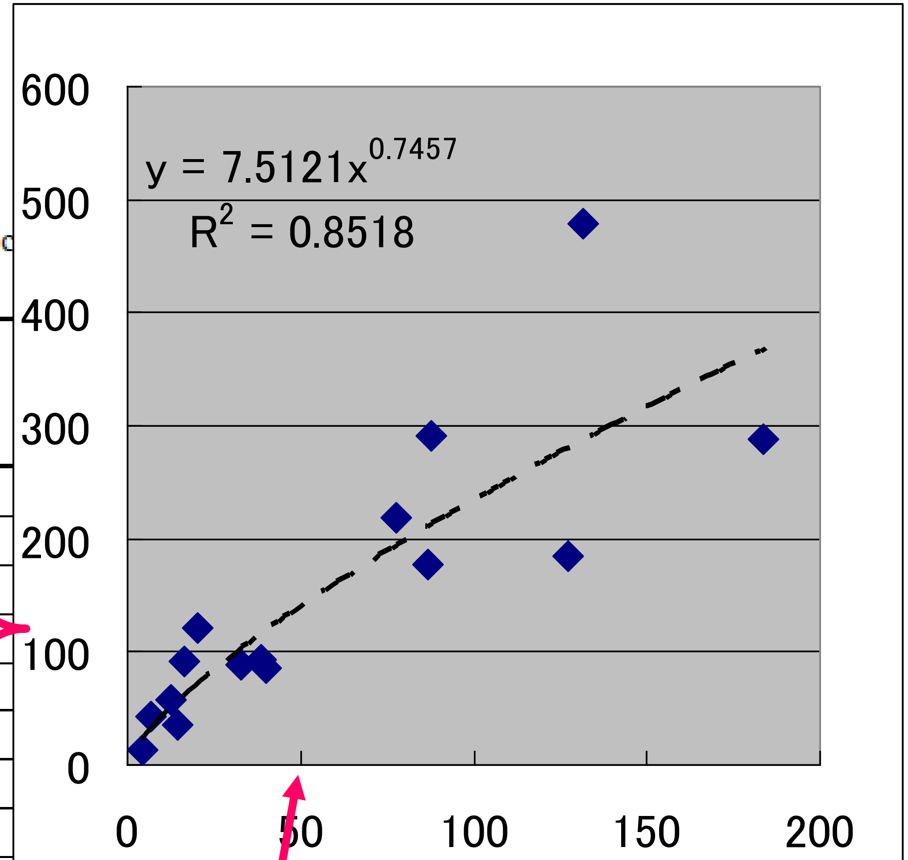
- high dose = definitive effect
- low dose = stochastic/probabilistic effect

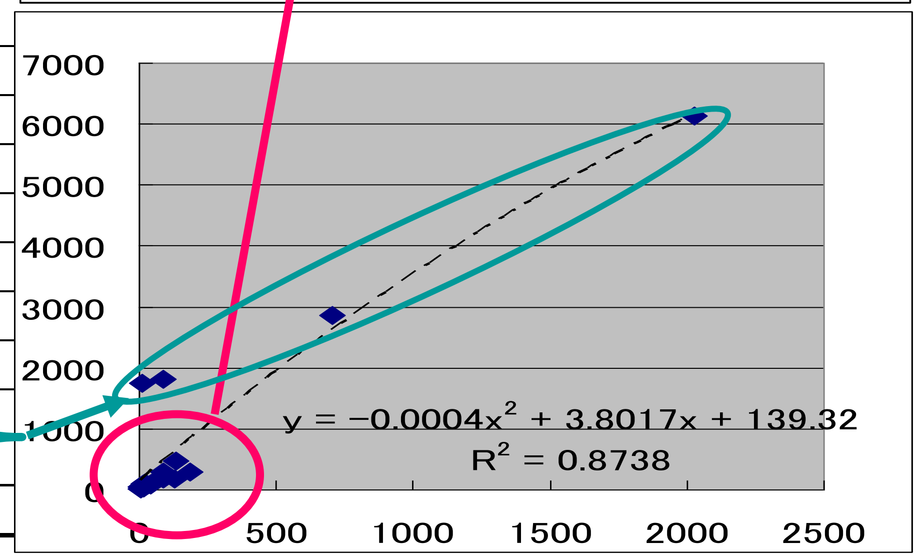
- **Low dose exposure**
  - No acute symptoms:
  - Dose-dependent increase in incidence of hepatic cancer

Low dose aflatoxin

Epidemiology data

Country	Region	AFB1 intake (ng/kg b.w. per day)	Liver cancerRate/year[a]
Kenya[b]	Highland	4.2	14
Kenya	Midland	6.8	43
Kenya	Lowland	12.4	58
Swaziland[c]	High veldt	14.3	35
Swaziland	Middle veldt	40.0	85
Swaziland	Lebombo	32.9	89
Swaziland	Low veldt	127.1	184
Transkei [d]	Four districts	16.5	91
Mozambique	Manhica-Mangud	20.3	121
Mozambique	Massinga	38.6	93
Mozambique	Inhambane	77.7	218
Mozambique	Inharrime	86.9	178
Mozambique	Morrumbene	87.7	291
Mozambique	Homoine-Maxixe	131.4	479
Mozambique	Zavala	183.7	288
China[e]	Guangxi B	11.7	1,754
China	Guangxi B	90.0	1,822
China	Guangxi C	704.5	2,855
China	Guangxi D	2,027.4	6,135



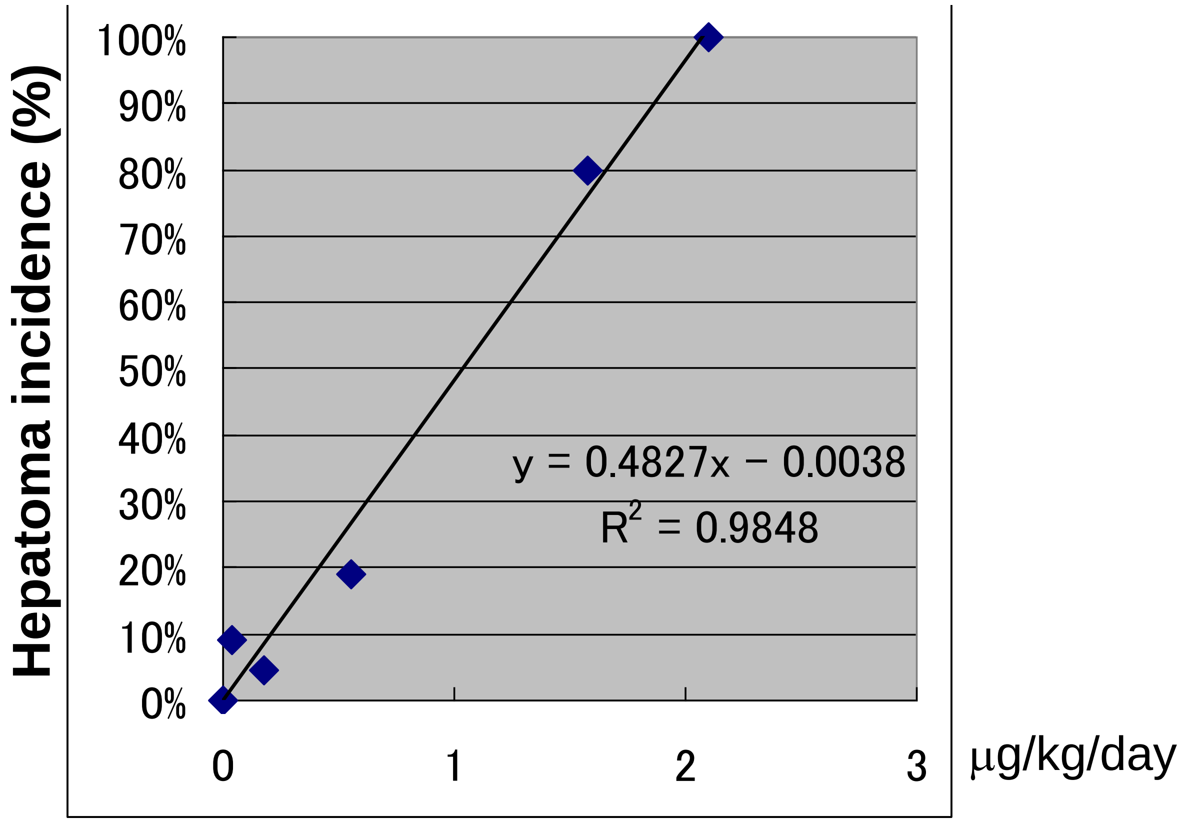


Low dose aflatoxin:

Experimental

Table 41: Induction of liver cell hyperplasia and tumours (hepatocellular carcinomas) in male Fisher rats after dietary administration of AFB1 (Wogan *et al.*, 1974).

Dose µg/kg b.w./day	Duration of dosing	Time adjusted dose	Tumour incidence	Hyperplasia	Transitional cells
0	104 w	0	0/18	1/18	0/18
0.04	104 w	0.040	2/22	6/22	1/22
0.2	93 w	0.179	1/22	4/22	1/22
0.6	96 w	0.554	4/21	13/21	0/21
2.0	82 w	1.58	20/25	8/25	7/25
4.0	54 w	2.1	28/28	8/28	4/28



RADIATION RESEARCH **160**, 376–379 (2003)

No Lengthening of Life Span in Mice Continuously Exposed to Gamma Rays at Very Low Dose Rates

S. Tanaka,[a,1] I. B. Tanaka, III,[a] S. Sasagawa,[a] K. Ichinohe,[a] T. Takabatake,[a] S. Matsushita,[b] T. Matsumoto,[a] H. Otsu[a] and F. Sato[a]

[a] *Department of Radiobiology, Institute for Environmental Sciences. 1-7, Ienomae, Obuchi* Rokkasho-mura, *, Aomori 039-3212, Japan; and* [b] *Laboratory of Animal Development and Research Group, National Institute of Radiological Sciences. 4-9-1, Anagawa, Inage-ku, Chiba-shi, Chiba 263-8555, Japan*

A total of 4000 (2000 per sex) specific-pathogen-free (SPF) B6C3F1

four groups of 1000 (500 per sex)

^{137}Cs γ rays approximately 400 consecutive days

daily doses of 21 mGy, 1.1 mGy and 0.05 mGy.

Student's or Welch's *t* test with the level of significance set at $P < 0.05$ (two-tailed test), depending on the homogeneity of variances between the two groups.

TABLE 1
Effects of Continuous Gamma-Ray Exposure on the Survival of SPF B6C3F1 Mice

Dose rate[a] (mGy day^{-1})	Average irradiation period ± SE[b] (days)	Total dose (mGy)	Number of mice[c]	Mean life span ± SE (days)	Life shortening ± SE (days)
Males					
0	0	0	498 (2)	912.7 ± 8.2	
0.05	402.3 ± 2.4	20	495 (5)	905.8 ± 8.3	6.9 ± 11.7
1.1	398.0 ± 2.1	400	500	895.2 ± 8.2	17.5 ± 11.6
21	404.8 ± 2.4	8000	499 (1)	812.0 ± 7.6**	100.7 ± 11.2**
Females					
0	0	0	500	860.5 ± 6.3	
0.05	402.3 ± 2.4	20	495 (5)	851.8 ± 6.7	8.7 ± 9.2
1.1	398.0 ± 2.1	400	497 (3)	839.8 ± 7.5*	20.7 ± 9.8*
21	404.8 ± 2.4	8000	500	740.9 ± 6.8**	119.6 ± 9.3**

Note: Mice were 8 weeks old at the beginning of irradiation.

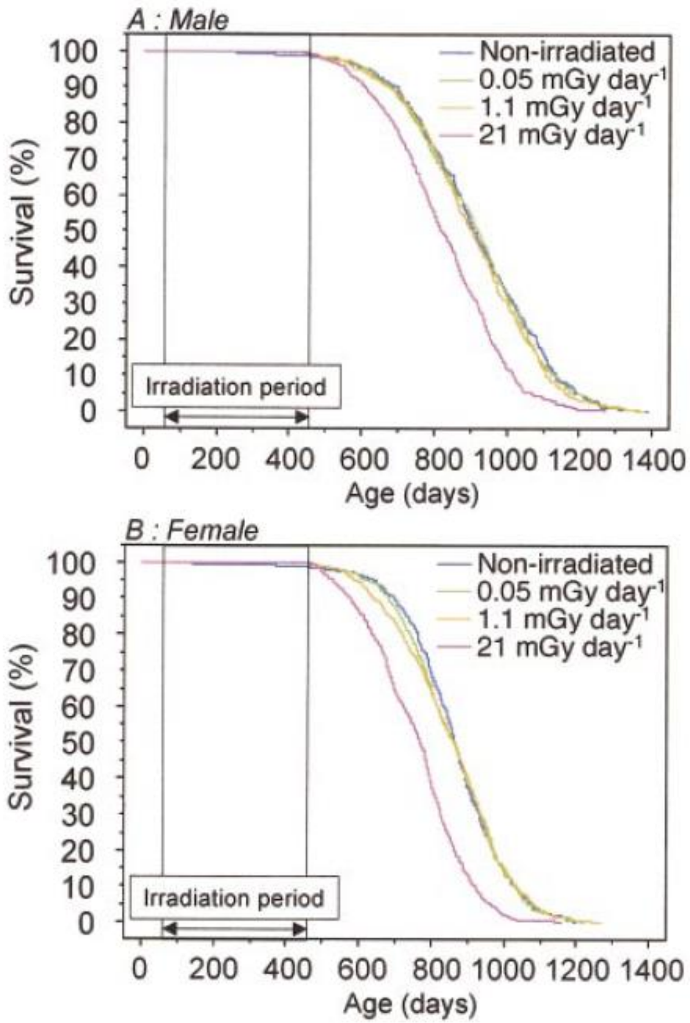


FIG. 1. Survival curves for B6C3F1 mice.

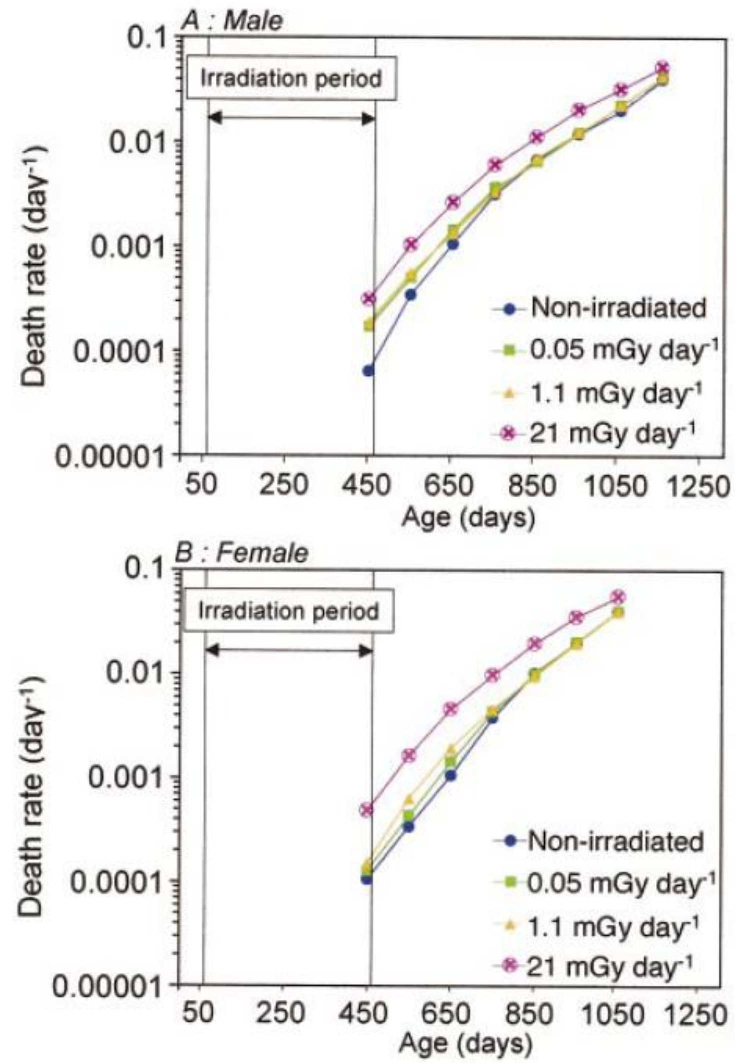
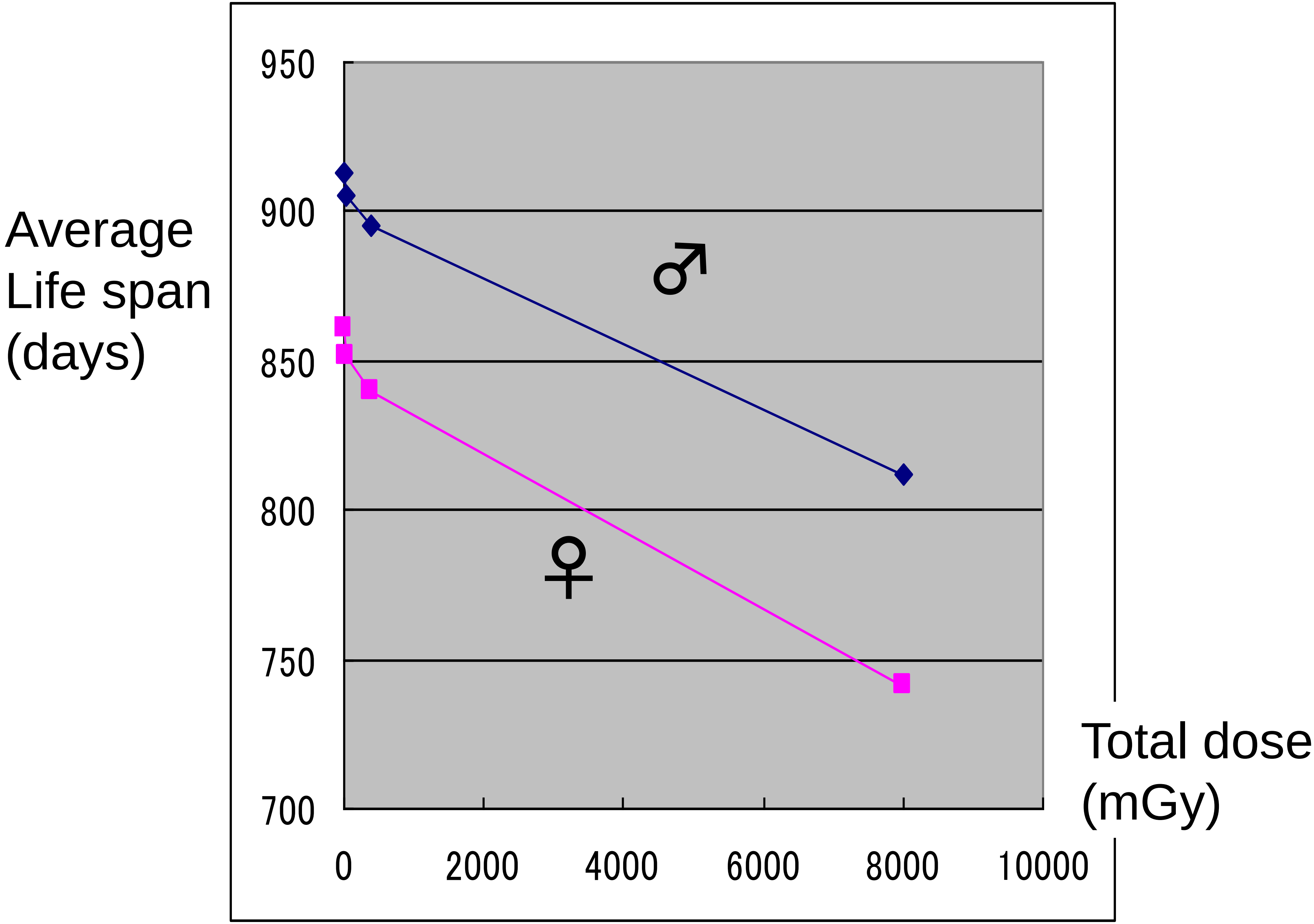


FIG. 2. Death rates of B6C3F1 mice.

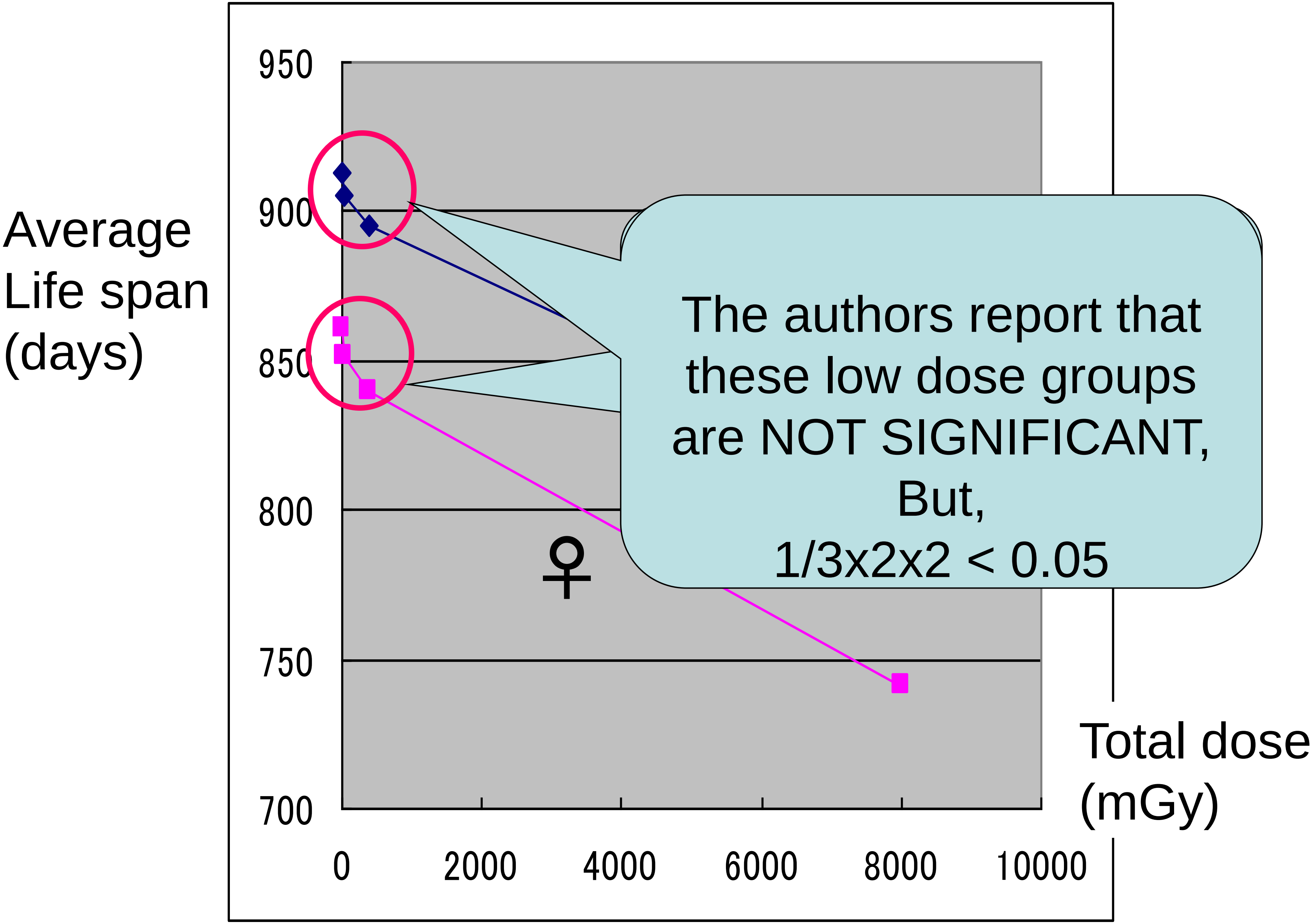
Gompertz plots

Gompertz plots

- contraction of the time axis (accelerated aging)
- shift of the time axis (premature aging)



Average
Life span
(days)
950
900
850
800
750
700
♂
♀
0
2000
4000
6000
8000
10000
Total dose
(mGy)



Average
Life span
(days)
950
900
850
800
750
700
0
2000
4000
6000
8000
10000
♀
Total dose
(mGy)
The authors report that
these low dose groups
are NOT SIGNIFICANT,
But,
1/3x2x2 < 0.05

Hormesis does not occur without a condition(=something to take care)

- Basal disease + Additional treatment

- When the mechanism of (B) and (A) is similar, the combined effect is additive, and therefore hormesis effect is not observed.

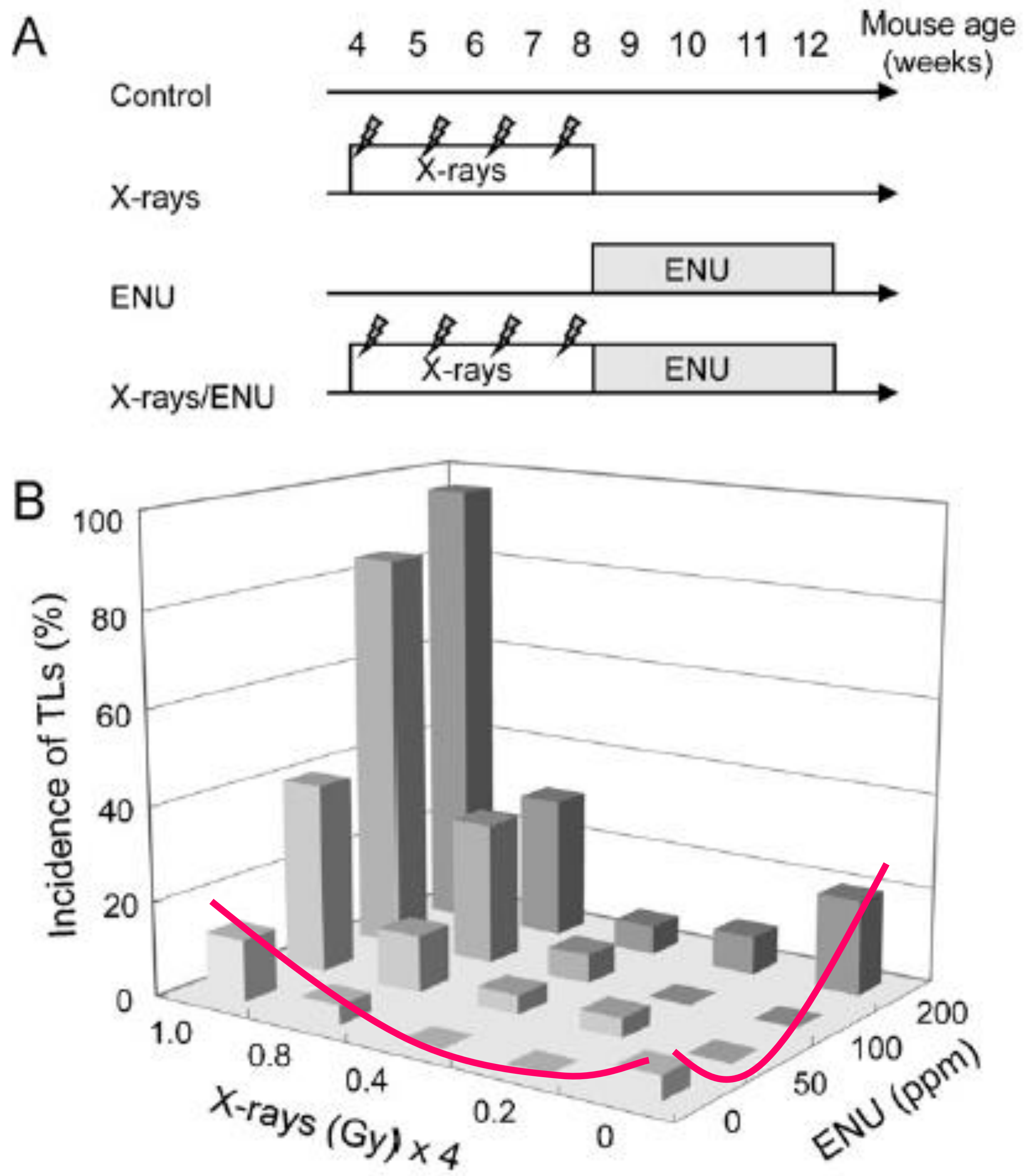
- Tanaka et al. 2003, 2007 can be interpreted that the ^{137}Cs γ-ray is additive to background natural radiation in terms of total cancer and longevity.

Combined exposure to X-irrac
treatment alters the frequency
T-cell lymphoma

Shizuko Kakinuma[a,*], Mayumi Nishin
Satomi Sudo[a], Yi Shang[a], Kazutaka Do

[a] *Radiobiology for Children's Health Research Program, Research Ce*
Japan
[b] *Regulatory Sciences Research Program, Research Center for Radic*

Mutation Research 737 (2012) 43–50



Tickle dose

J. Radiat. Res., 50, 401–405 (2009)

Review

Low-dose Radiation Attenuates Chemical Mutagenesis *In Vivo*#

–Cross Adaptation–

Shizuko KAKINUMA*, Kazumi YAMAUCHI, Yoshiko AMASAKI,
Mayumi NISHIMURA and Yoshiya SHIMADA

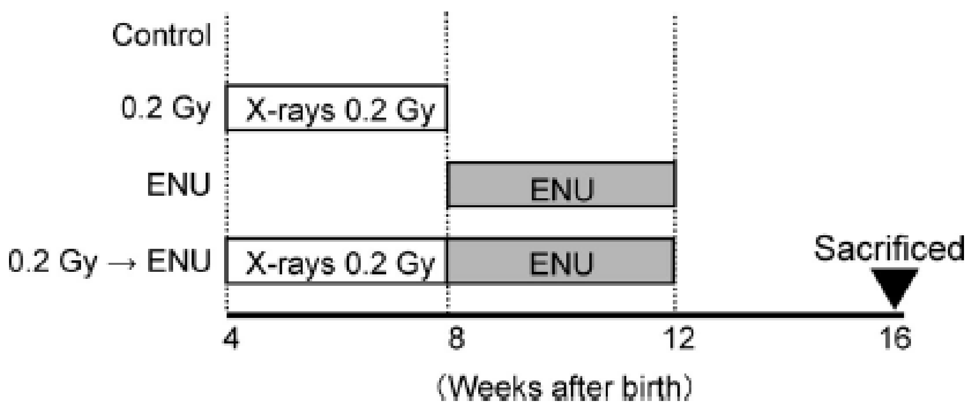


Fig. 1. Experimental design for *gpt* mutation analysis of thymic DNA from mice treated with X-rays, ENU or a combination of the two. Mice were exposed to X-rays weekly for 4 weeks. ENU was administered at a concentration of 200 ppm in drinking water.

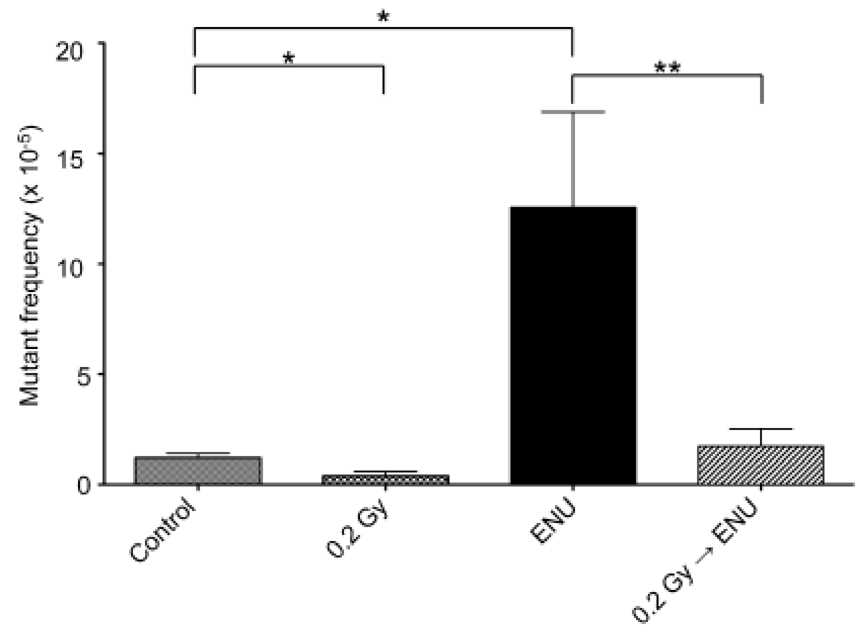


Fig. 2. Mutant frequency analysis of *gpt* recovered from thymus DNA from control, irradiated (0.2 Gy × 4), ENU-treated, and irradiated/ENU-treated mice. *$P < 0.05$, significantly different from control. **$P < 0.05$, significantly different from ENU. Bars represent mean ± S.D.

Mithridates VI Eupator
The Royal Toxicologist

(120-63 BC) King of Pontus
aka Mithridates the Great

Slide by
Bruce Blumberg
UC Irvine

radiation

- DNA damage
- Protein damage

●Reversible effects

<u>■Irreversible effects</u>

View Point (3)

Radiation DNA damage

■irreversible = non-repaired

Radiation Protein damage

■irreversible = repair signal-induced epigenetic changes

Basis:

epigenetic modification alone can cause tumor (example: iPS)

Hiroshima/Nagasaki

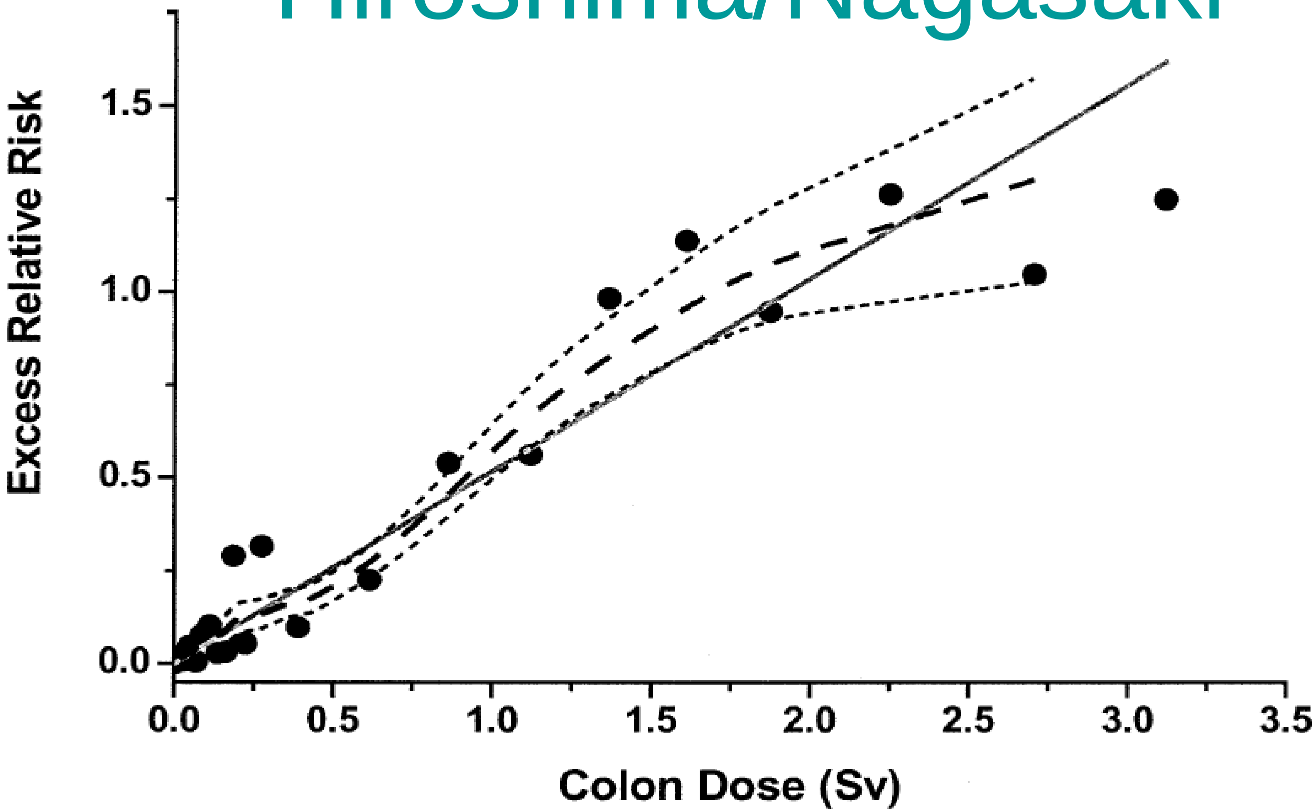


FIG. 2. Solid cancer dose–response function averaged over sex for attained age 70 after exposure at age 30. The solid straight line is the linear slope estimate, the points are dose category-specific ERR estimates, the dashed curve is a smoothed estimate derived from the points. The dotted curves indicate upper and lower one-standard-error bounds on the smoothed estimate.

Solid cancer ≒ other than leukemia

survivo
ERR pe
1.5). Tl
respons
cantly 1
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Age-De

Since
age and
sen to e
to vary
ever, w
model u
to vary
contrast
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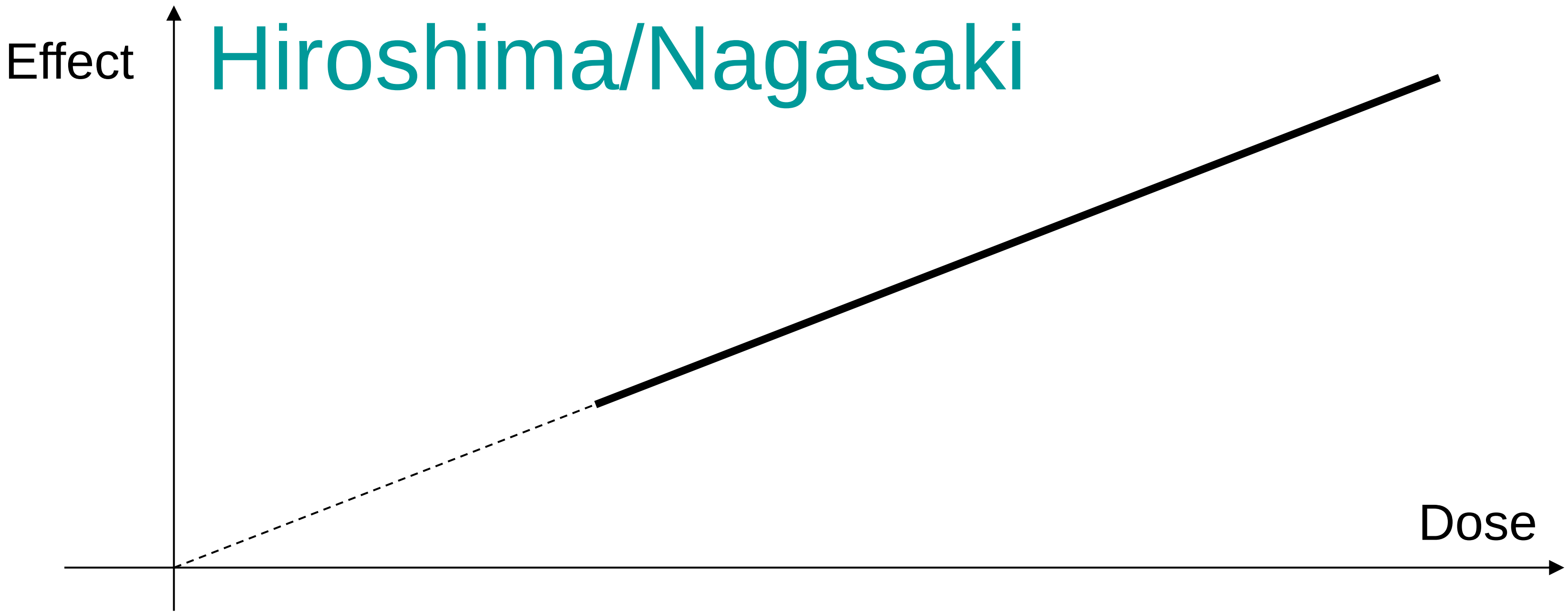
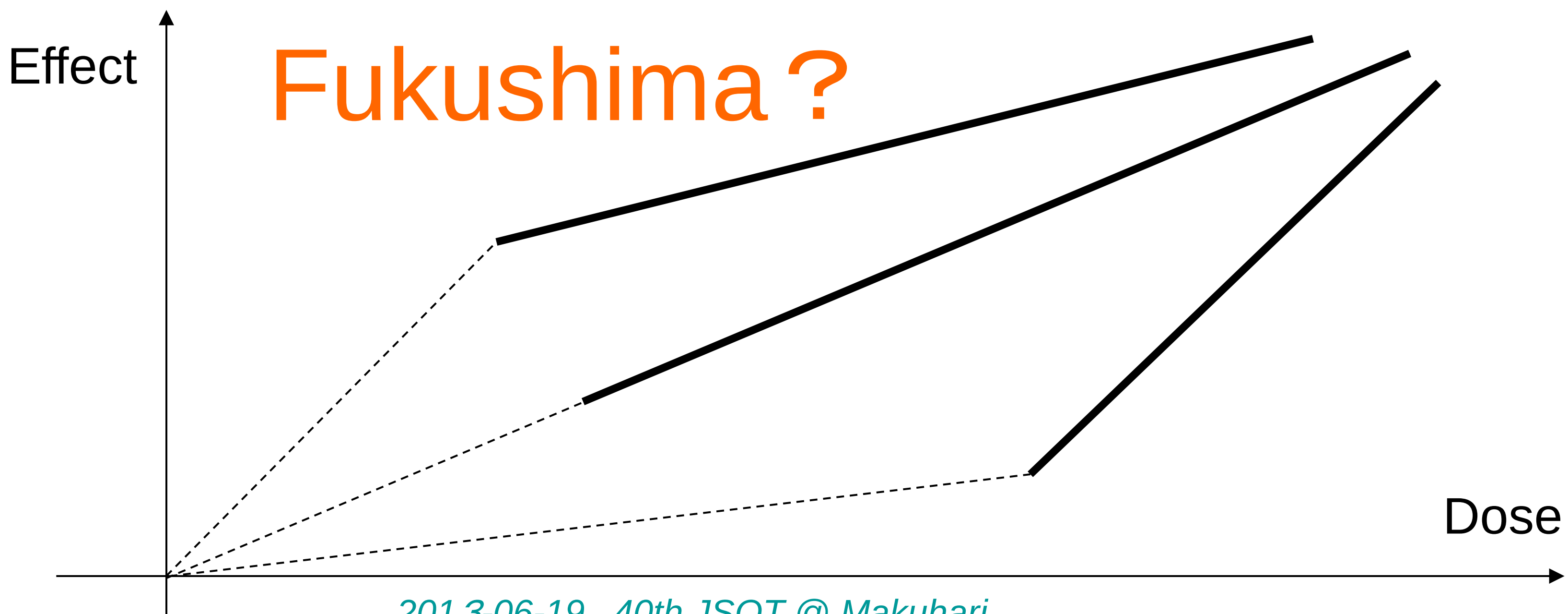

Effect
Hiroshima/Nagasaki
Dose

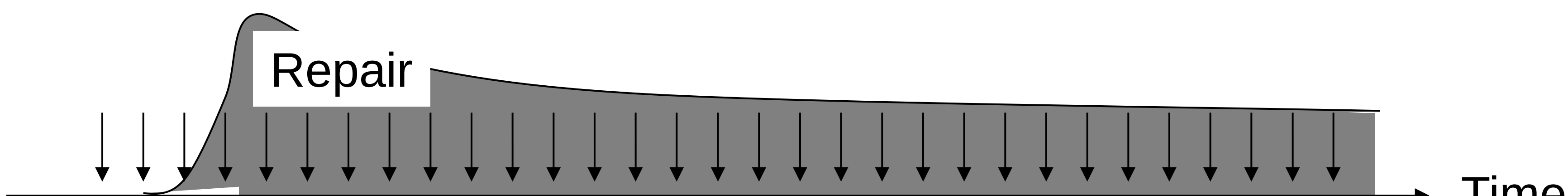

Effect
Fukushima？
Dose

Hiroshima/Nagasaki

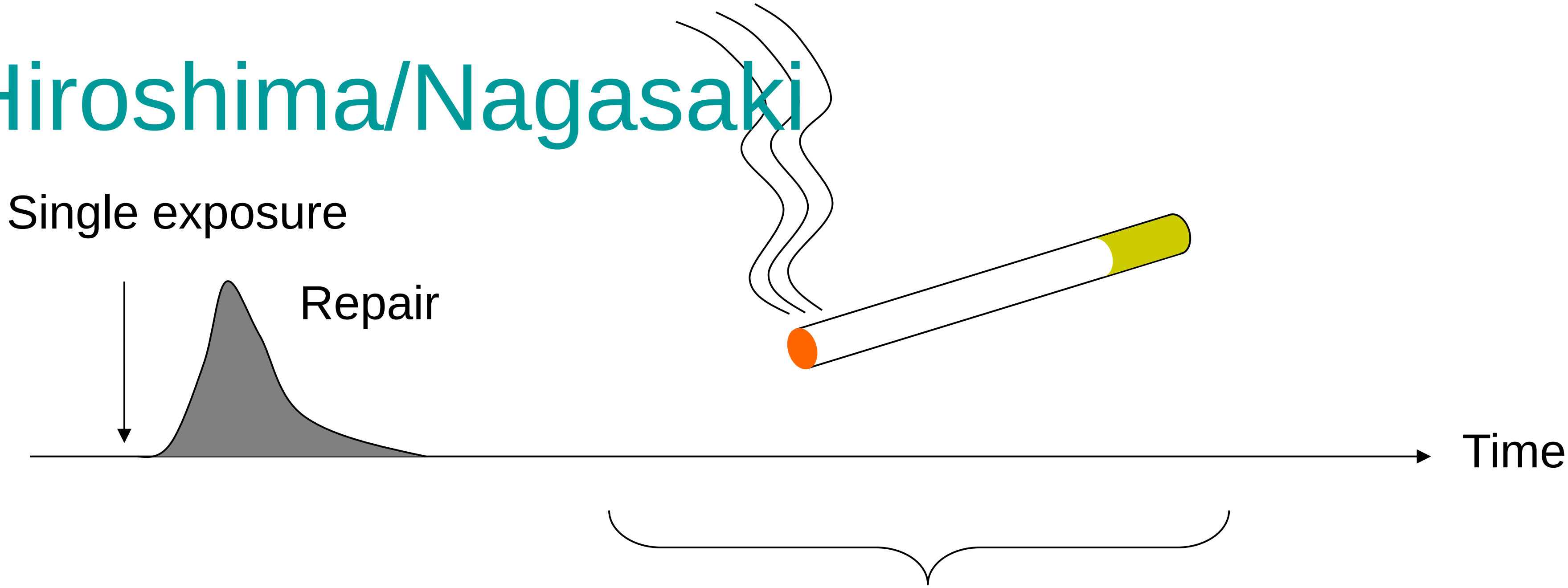
Single exposure

Fukushima

Repeated or continuous exposure



Hiroshima/Nagasaki



Light smoker ⇒ synergistic effect on Lung Cancer

★Toxicologically speaking：

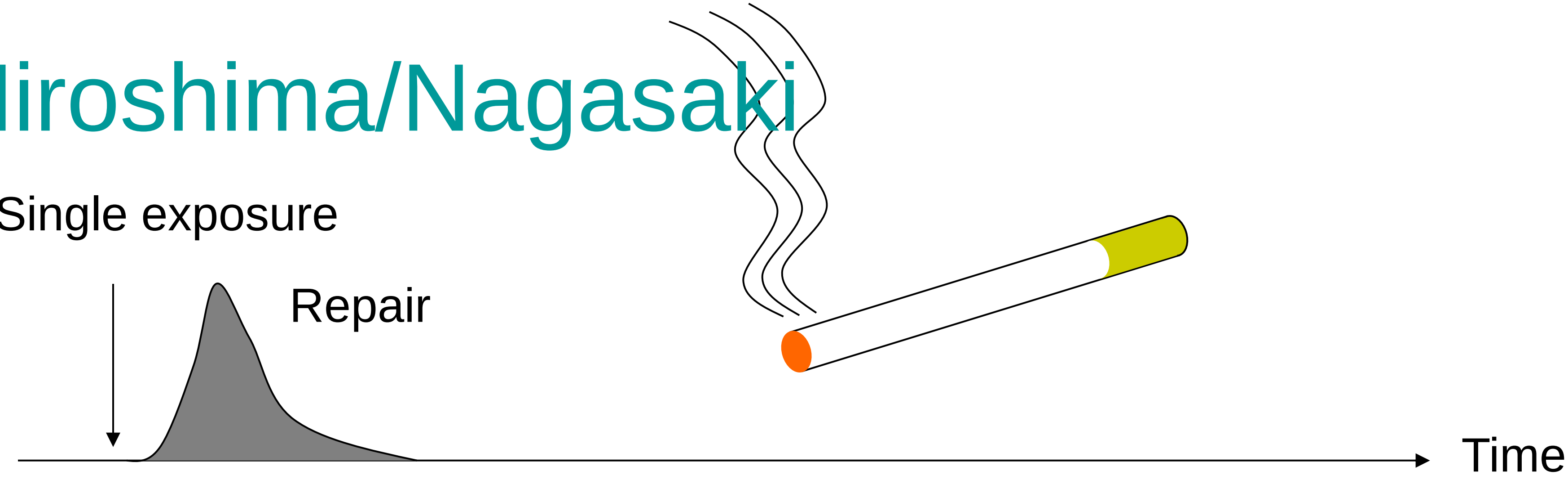
A-bomb was the cancer initiator

Smoking was the cancer promoter

Heavy smoker ⇒ clear induction of lung cancer regardless of radiation

⇒ heavy smoking masks the radiation effect

Hiroshima/Nagasaki



RADIATION RESEARCH **174**, 72–82 (2010)
0033-7587/10 $15.00

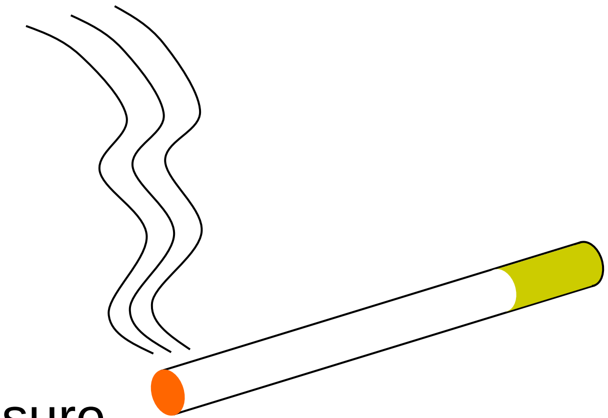
DOI: 10.1667/RR2083.1

Radiation and Smoking Effects on Lung Cancer Incidence among Atomic Bomb Survivors

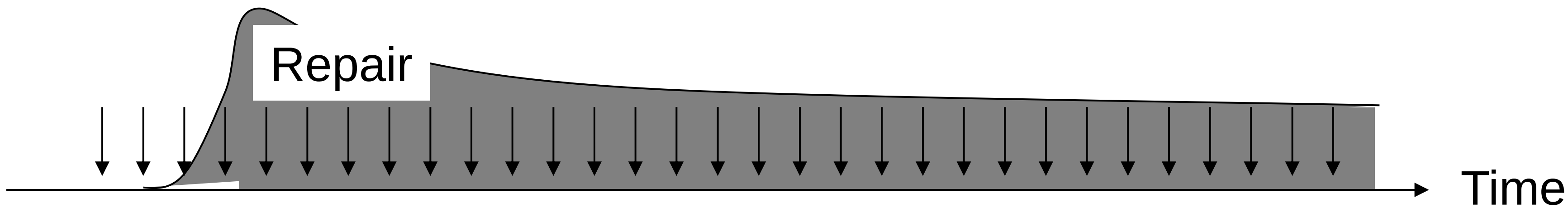
Kyoji Furukawa,[a,1] Dale L. Preston,[b] Stefan Lönn,[c] Sachiyo Funamoto,[a] Shuji Yonehara,[d] Takeshi Matsuo,[e] Hiromi Egawa,[f] Shoji Tokuoka,[a] Kotaro Ozasa,[a] Fumiyoshi Kasagi,[a] Kazunori Kodama[a] and Kiyohiko Mabuchi[g]

[a] Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan; [b] Hirosoft International, Eureka, California; [c] Karolinska Institutet, Stockholm, Sweden; [d] Welfare Association Onomichi General Hospital, Japan; [e] Nagasaki Health Promotion Corporation, Nagasaki, Japan; [f] Hiroshima City Asa Hospital, Hiroshima, Japan; and [g] Division of Cancer Epidemiology & Genetics, National Cancer Institute, Bethesda, Maryland

Fukushima

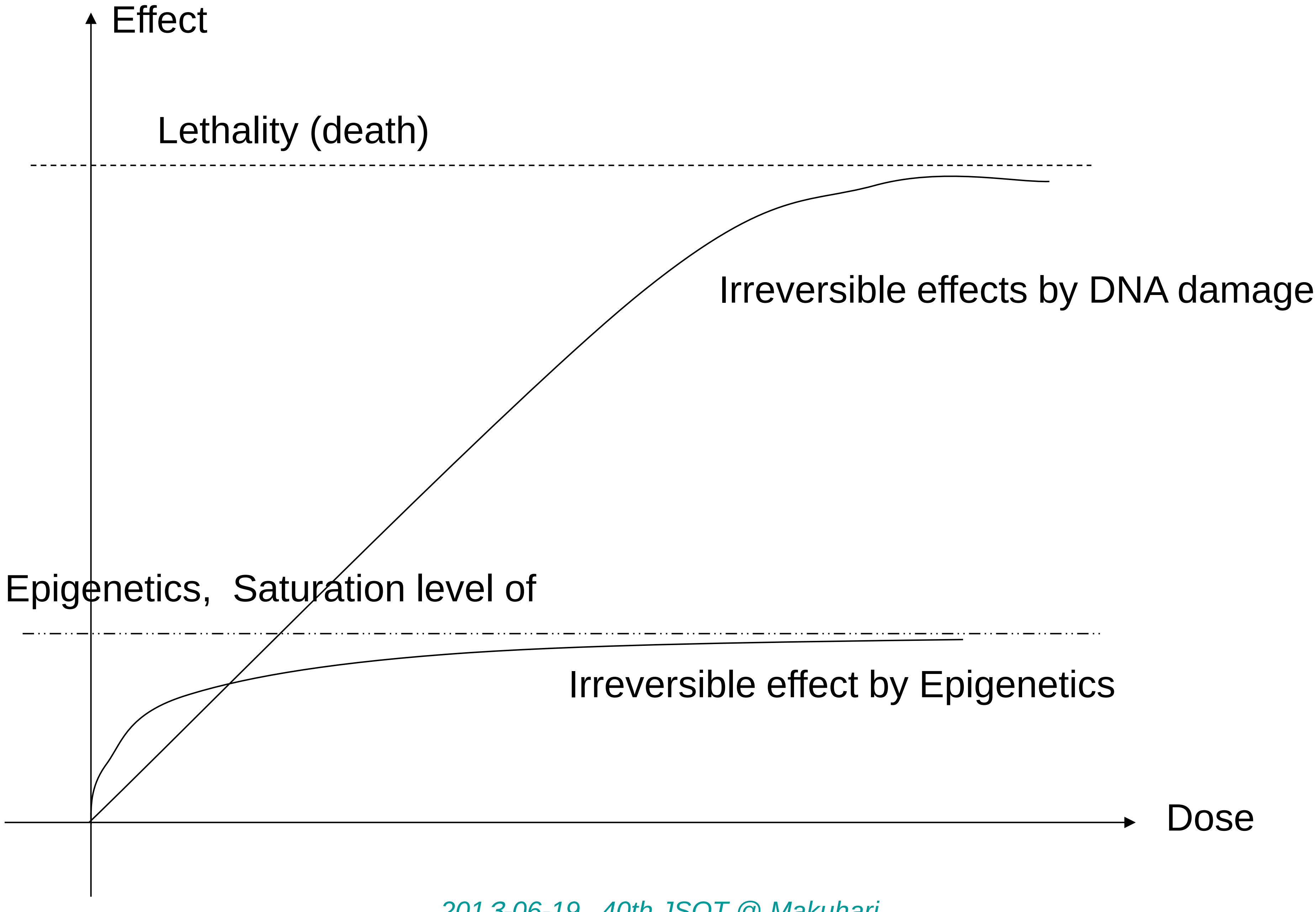


Repeated or continuous exposure



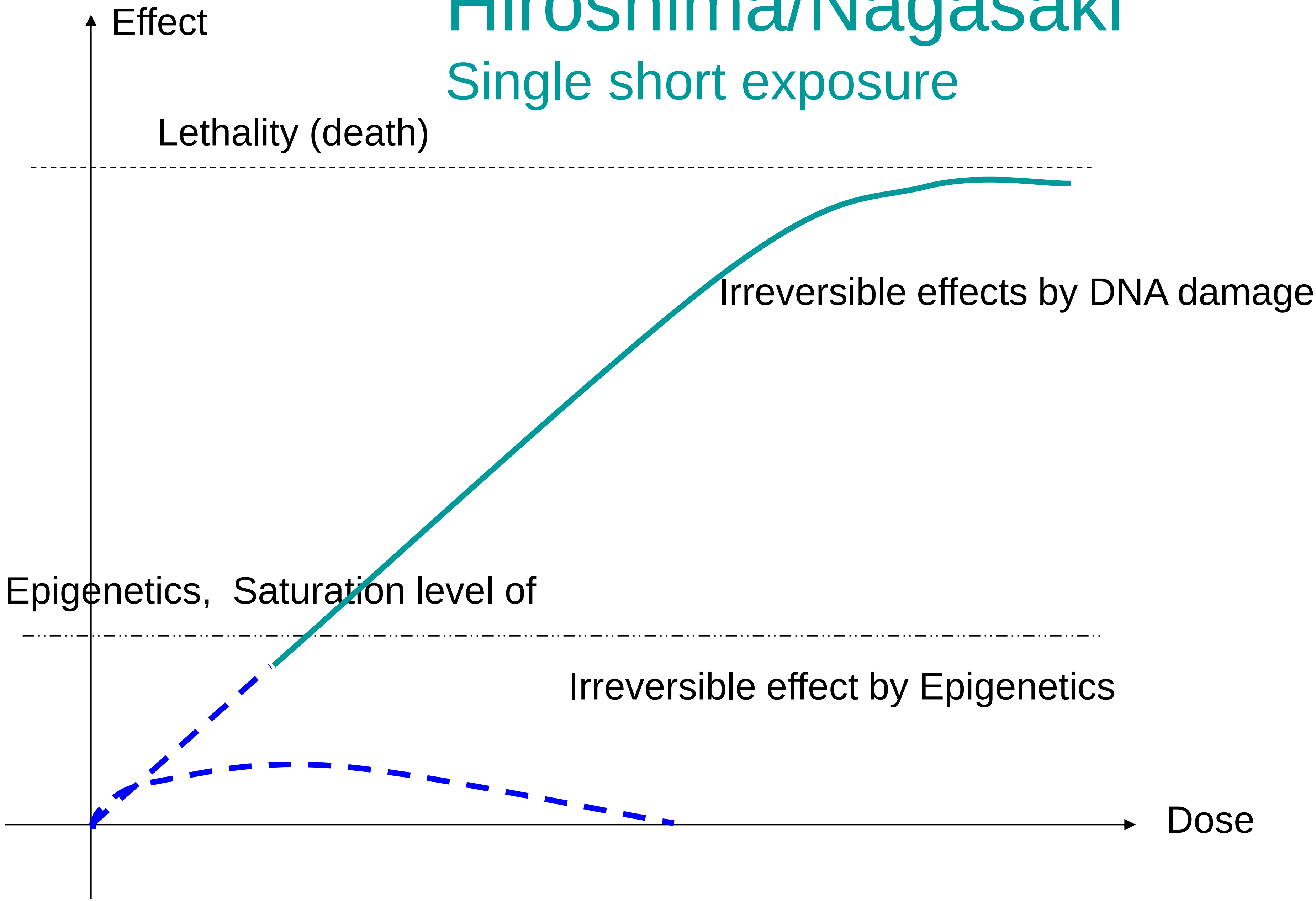
?

What happens to those who work during day for decontamination and come back to a hotel and smoke for relaxation?


Effect
Lethality (death)
Irreversible effects by DNA damage
Epigenetics, Saturation level of
Irreversible effect by Epigenetics
Dose

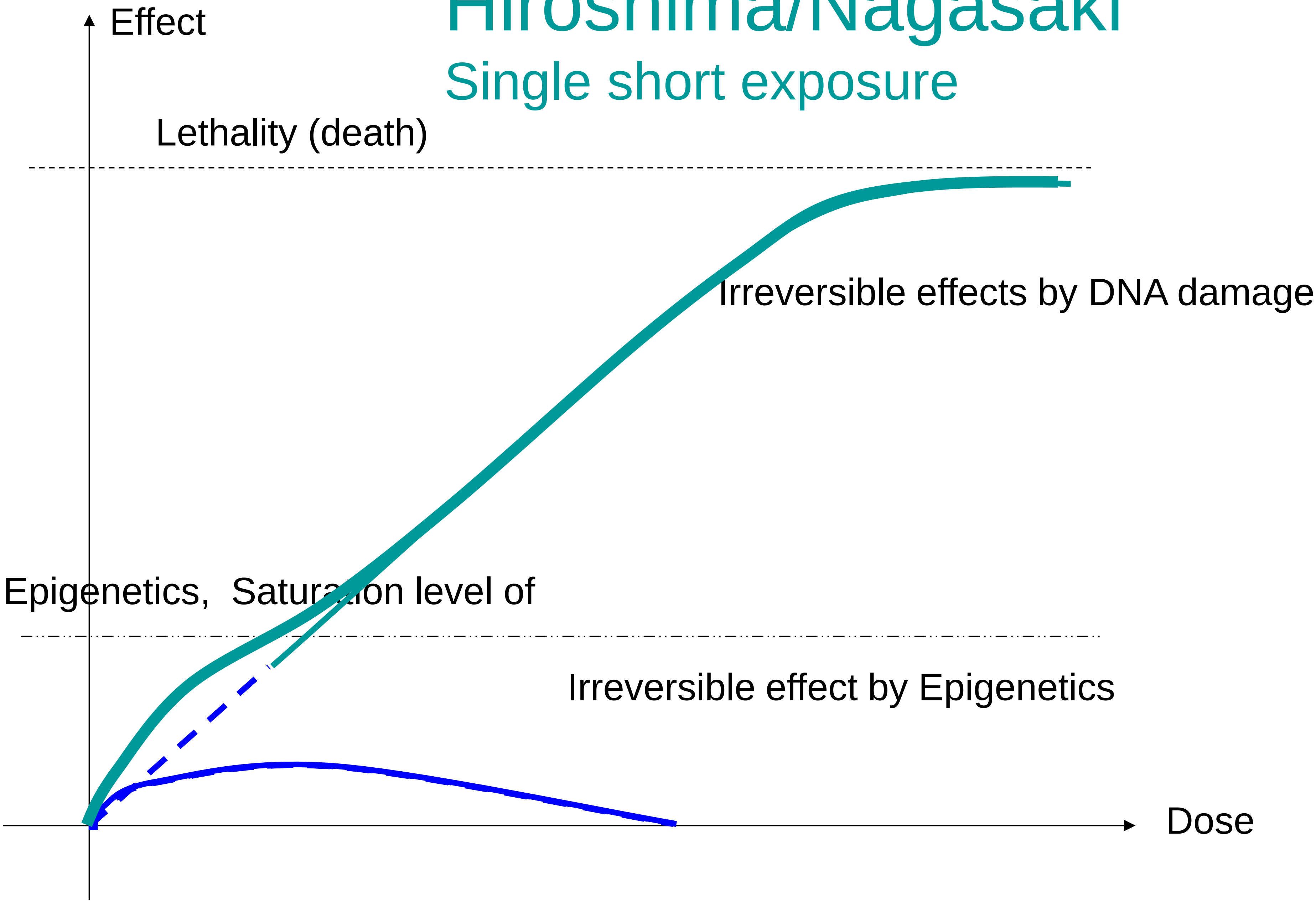
Hiroshima/Nagasaki

Single short exposure



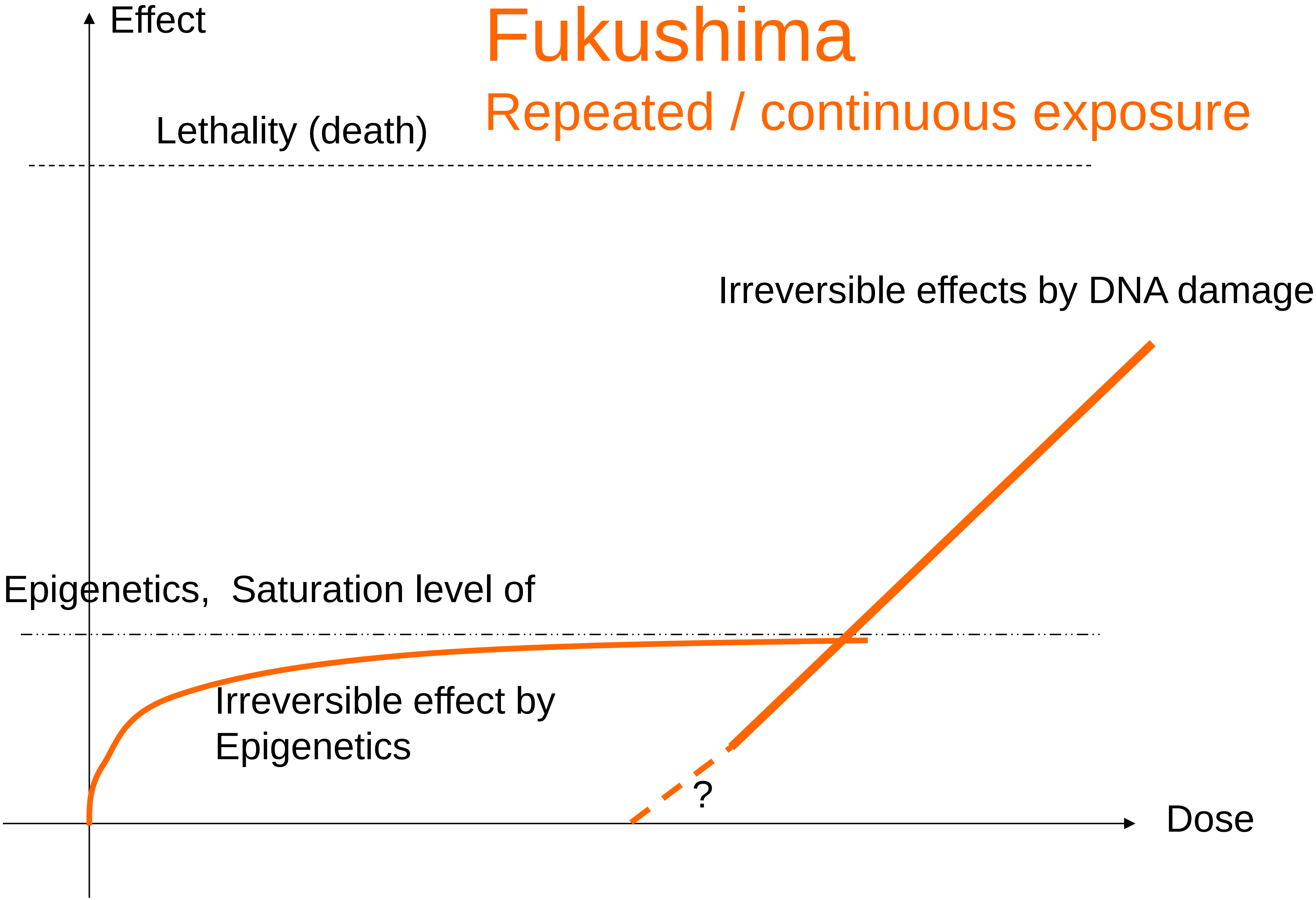
Hiroshima/Nagasaki

Single short exposure



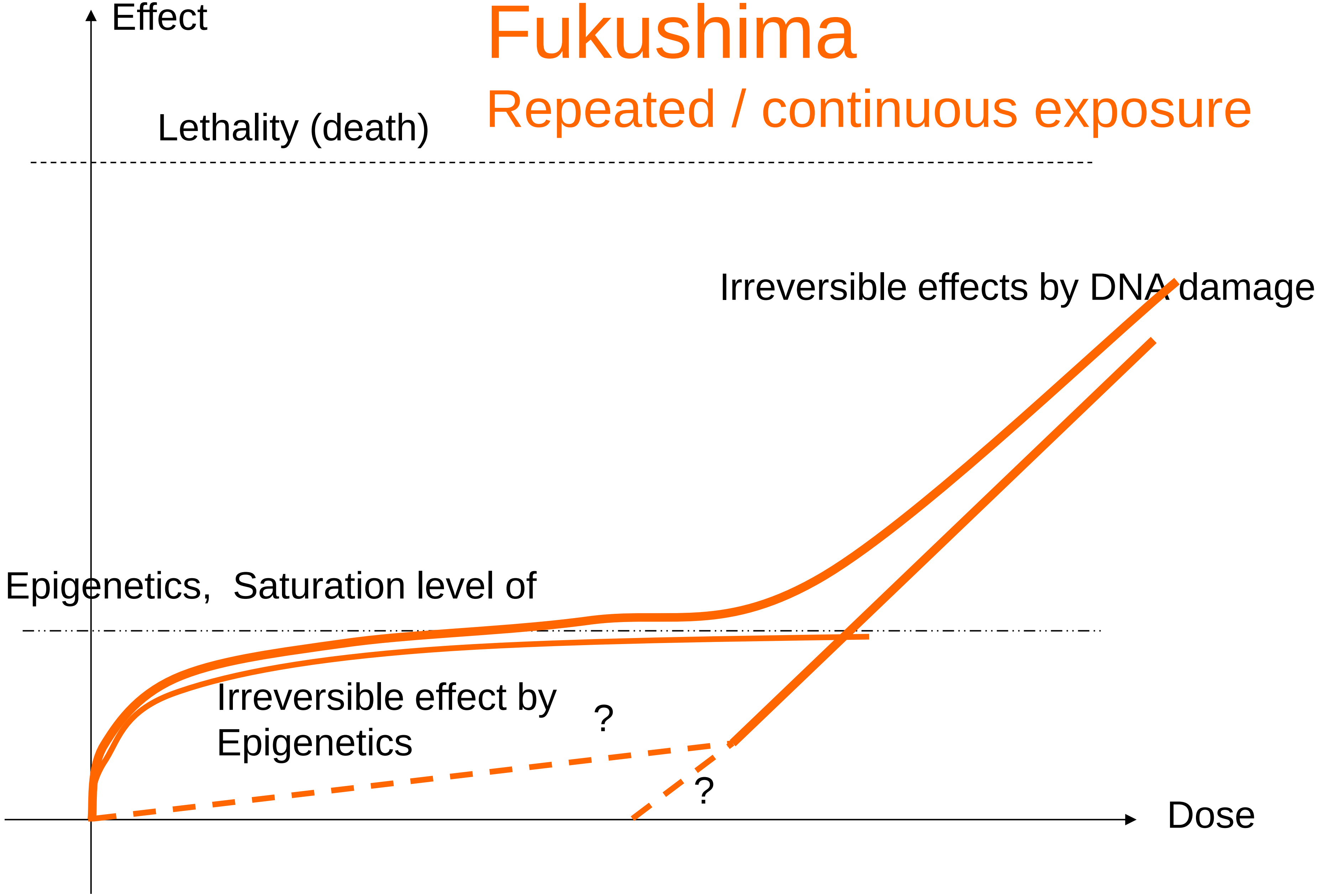
Fukushima

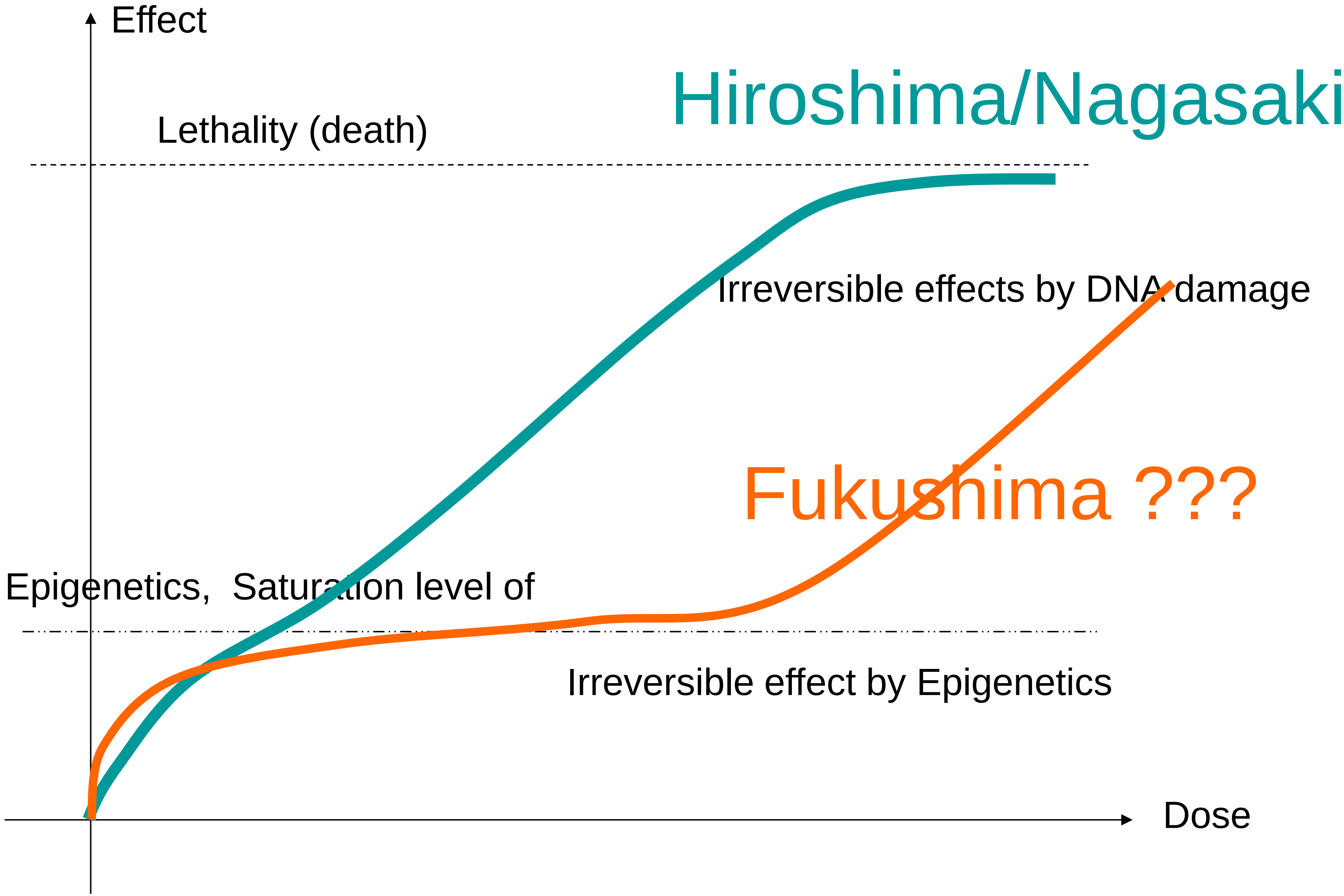
Repeated / continuous exposure



Fukushima

Repeated / continuous exposure




Effect
Hiroshima/Nagasaki
Lethality (death)
Irreversible effects by DNA damage
Fukushima ???
Epigenetics, Saturation level of
Irreversible effect by Epigenetics
Dose

Research direction, proposal

- Re-establishment of Radiation Toxicology
  - Genetic irreversible effect
    - Low organ specificity
  - Epigenetic irreversible
    - High organ specificity
- Commonality of radiation and chemical signaling effect
  - Sensing systems of Chemical reaction (incl. that of ionizing radiation)

J. Radiat. Res., 50, 241–252 (2009)

Microarray Analysis of Differentially Expressed Genes in the Kidneys and Testes of Mice after Long-term Irradiation with Low-dose-rate γ-rays

Keiko TAKI[1], Bing WANG[1], Tetsuo NAKAJIMA[1], Jianyu WU[1], Tetsuya ONO[2], Yoshihiko UEHARA[2], Tsuneya MATSUMOTO[3], Yoichi OGHISO[3], Kimio TANAKA[3], Kazuaki ICHINOHE[3], Shingo NAKAMURA[3], Satoshi TANAKA[3], Junji MAGAE[4], Ayana KAKIMOTO[1] and Mitsuru NENOI[1*]

RADIATION RESEARCH 174, 611–617 (2010)

Gene Expression Profiles in Mouse Liver after Long-Term Low-Dose-Rate Irradiation with Gamma Rays

Yoshihiko Uehara,[a,1] Yasuko Ito,[a] Keiko Taki,[b] Mitsuru Nenoi,[b] Kazuaki Ichinohe,[c] Shingo Nakamura,[c] Satoshi Tanaka,[c] Yoichi Oghiso,[c] Kimio Tanaka,[c] Tsuneya Matsumoto,[c] Tatjana Paunesku,[d] Gayle E. Woloschak[d] and Tetsuya Ono[a]

Overall Conclusion

- Risk assessment of Low dose rate repeated/continuous exposure needs data on epigenetic effects of radiation
  - Different responses by adults, children, infants, embyro, germ cells.
  - highly organ/tissue specific

Acknowledgement

This presentation is a result of continuing discussion among
Drs.
Otsura Niwa
Michiaki Kai
Taisei Nomura
Mamoru Nomura
Ikuo Horii
Akihiko Hirose, and others, and
staffs of Div. Cell Mol Tox of NIHS


END

What is $p<0.05$

When you play chess game with a person you think equal,,,

- If you lose 3 times in a row, you start to think you are weaker.
- If you lose 4 times in a row, you think you may be weaker
- If you lose 5 times in a row, you will surely give up.

- The probability that you lose 4 times in a row is
  $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = 1/16 = 0.0625$
- The probability that you lose 5 times in a row is
  $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = 1/32 = 0.03125$

$P<0.05$ is such a number!

A disease “Significantosis”

by Akira Sakuma (U Tokyo, Japan)

The symptom of this “disease” is that once the “patient” is confronted with a data set with a p-value smaller than 0.05, then he or she instantly believes that it is definitely biologically significant, and vice versa, i.e. if not statistically significant, then instantly believes that it is definitely biologically not significant.

Prof. Sakuma says that “statistically significant” dose not contain that it is biologically and medically significant. Even if it is not statistically significant, it is not actively proven that the parent population is different, but suggestive of no difference for the time being.

Akira Sakuma, Drug efficiency evaluation-Planning and analysis –I, Unversity of Tokyo Press,1977, pp51.