5-2. Approach for Risk Management for Environmental Impacts of Pharmaceuticals

5-2-1. Perspectives on Environmental Impacts of Pharmaceuticals

Pharmaceuticals for human use are intended to be administered to humans and potential risks posed by the administered pharmaceuticals on human health are already thoroughly assessed during examination of the application for their approval. Furthermore, the possibility of the amount of exposure to a particluar pharmaceutical discharged into the environment exceeding the dose at which it is used in clinical practice is expected to be minimal. Accordingly, there may be no need for special consideration on the potential risks posed by pharmaceuticals to human health via the surrounding environment.

The potential risks posed by pharmaceuticals to human health are assessed on the basis of toxicity data obtained in laboratory animals, considering the species differences between humans and the animal species chosen for the toxicological studies. That is, humans are assumed to be more sensitive to the pharmaceutical tested than the animal species. Considering the diversity of environmental organisms, there may be cases where the environmental organisms are more sensitive to a particular pharmaceutical than humans. Consequently, the current procedure for examination of pharmaceuticals intended to assess their potential risks posed to human health may not always be sufficient for assessment of the potential risks to environmental organisms. This is why assessment of the environmental risk posed by pharmaceuticals should be additionally called for in examination of the application for their approval.

Highlighting "restriction of use" as the key principle in risk management of pharmaceuticals appears to be reasonable, when comparing with the approaches used for risk management of other chemical substances. Pharmaceuticals have a unique feature that does not apply to the majority of other chemical substances: they often generate metabolites with biological activities. Therefore, both pharmaceuticals and their metabolites should be subjected to risk assessment.

5-3. Examination Procedure for Pharmaceuticals Involving Environmental Impact Assessment

5-3-1. Organization for Assessment

In Japan, examination of application for approval of pharmaceuticals is conducted first by the Pharmaceuticals and Medical Devices Agency (PMDA) and finally by Pharmaceutical Affairs and Food Sanitation Council (PAFSC). The current procedure for this examination

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involves the following steps as defined by related regulations (see Annex 9 for details):

1) Notification of clinical trial protocol to PMDA (required when drug development by the applicant reaches the stage of start of a clinical trial)

2) Consultation on the clinical trial protocol by PMDA (in response to the applicant's request for advice on the clinical trial)

3) Application for approval of a new drug (when the applicant has completed collection of the data to be attached to application for approval of a new drug)

4) Review by review experts and inspection experts at PMDA

5) Expert review conference (held to request opinions of invited external experts in the related fields)

6) Final review by PAFSC

7) Post-marketing safety survey

8) Post-marketing clinical trial (whenever required)

9) Reexamination

Thus, the procedure for examination of pharmaceuticals by PMDA under PAFSC has been fully established, and it would, therefore, be not reasonable to develop a new dedicated examination system for the environmental risk posed by pharmaceuticals. Rather, it would be appropriate to call for submission of additional data needed for assessment of the environmental risk in addition to those for assessment of the risk to human health and review both .Environmental impacts of pharmaceuticals should be assessed and checked at each step of the procedure for examination of application for their approval. The following measures might be helpful:

1) Include environmental impacts of the pharmaceutical to be examined in items to be reported in the new drug application form;

2) Recruit and assign PMDA review experts experienced in assessment of the environmental impacts of pharmaceuticals;

3) Invite external experts with expertise in assessment of the environmental impacts of pharmaceuticals to join the expert review conference.

It would be also helpful to call for reporting of the amount of a particular drug produced or sold to the regulatory authority, whenever necessary, to enable implementation of effective environmental measures

5-3-2. Data required for Application of New Pharmaceuticals

In addition to data conventionally required for examination of new pharmaceuticals, data on the potential for exposure of and toxicity in environmental organisms essential to environmental risk assessment should also be called for. More specifically, information,

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such as the physicochemical properties, potential for exposure, degradability, bioconcentration, base set of ecotoxicity data, toxicity data obtained in top predators, and toxicity of metabolites, should be provided. A claim of qualification for exemption from the environmental risk assessment should be justified by appending relevant evidence .

5-3-3. Assessment Process

An environmental risk assessment process for pharmaceuticals is proposed by considering the approaches described in the preceding sections. The process is illustrated in detail in an assessment flow on a separate sheet and briefly summarized below in Table 5-3-3.

Table 5-3-3. A proposed environmental risk assessment process.

Step	Key question asked in assessment
1a	Qualifies for pharmaceuticals to be exempted from assessment (herbal medicinal products, diagnostic products, biological macromolecules, vitamines, electrolytes, amino acid, etc.)?
1b	Qualifies for pharmaceuticals with special circumstances to be exempted from assessment (low production volume under 0.2 ton/year, diagnostic products exclusively used in particular facilities, exclusively exported, exclusively used in a closed system and according to established criteria)?
2	Highly susceptible to biodegradation (degradation rate over 60%) and exempted from further testing for bioconcentrtation and ecotoxicity?
3	Bioconcentration factor (BCF) under 5000 (otherwise, classified as"highly susceptible to bioconcentrtation")?
4a,b	PEC under the reference level (0.01 µg/L)? ?
5a	PEC/PNEC ratio under 1?
5b,c	PEC potentially over the reference level in a particular environment but the PEC/PNEC ratio calculated from this PEC value under 1?
6	Refinement of PEC/PNEC possible?
7	Essential to human life and of public interest and consideration of exceptional control measures needed?

The key criteria for decision in the assessment flow presented are summarized as follows:

1) Is exemption from ecotoxicity data justified?
2) Is the target substance susceptible to biodegradation?
3) Is the target substance susceptible to bioconcentration?
4) Is the environmental risk a concern?
5) Does the target substance have the potential to pose envitonmental risk under a particular environment to be examined by additional tests?

Some of these criteria are clearly established at present, while others remain to be established following further discussion. Only clearly established criteria are applied to

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decision in the initial or preliminary assessment step.

The environmental risk assessment process for pharmaceuticals proposed in the present report involves tests for degradation/accumulation and those for ecotoxicity performed in tandem. That is, the former tests are required for all target substances clearing steps 1a and 1b in Table 5-3-1 for screening purpose and the latter required only for those classified as "highly susceptible to degradation/accumulation" based on the screening test results. In contrast, an alternative idea suggests that tests for degradation/accumulation and those for ecotoxicity should be performed in parallel, i.e., both tests should be performed unconditionally for all eligible target substances. This alternative assessment process could address such cases where pharmaceuticals highly susceptible to degradation in nature are used routinely in high volume, with a concern of persistence in the environment if the rate of their degradation is not high enough to balance the rate of their discharge into the environment. When the parallel assessment process design is adopted, the criteria for assessing degradation/accumulation should be defined more clearly. If the purpose of the tests for degradation/accumulation is limited to identification of pharmaceuticals highly persistent in the environment that need to be subjected to special regulatory measures, the criterion adopted in the original assessment process in Table 5-3-1 (BCF$\geq$5,000) can be used without modification. Some suggest that pharmaceuticals showing considerable persistence in the environment (e.g., 5,000>BCF$\geq$1,000) should also be subjected to some regulatory measures, different from those for substances exhibiting a higher persistence.

Step 8 (at the end of the entire assessment process, but not listed in Table 5-3-1) is intended to provide exceptional regulatory measures applicable to some pharmaceuticals that are essential to human life and of public interest (Step 7) but have been shown to pose potential risk to the environment (Steps 2 to 6): restrictions on use of such pharmaceuticals can be eased at least partly. At Step 8, the validity of application of such exceptional measures to a particular pharmaceutical product should be assessed considering the risk-benefit balance determined taking the actual situation of each product into account. As a consequence, the decision should be made on a case-by-case basis, in principle. In easing the restrictions on the use of eligible pharmaceuticals, maximum flexibility in defining the conditions in which they can be used (e.g., placing a limit on the amount used, defining justifiable usage, etc.) should be allowed and the decision should be made by a special committee composed of diverse members of the society, namely, experts, consumers, and industry.

5-3-4. Other Special Remarks

(1) Flexible assessment system

While environmental risk assessment is conducted according to the criteria prevalent at the time of application, the assessment procedure is subject to future change. For example, hormones are currently excluded from environmental risk assessment, because no testing methods are available for this purpose, but may well be expected to be included in the future when appropriate testing methods are established. Thus, pharmaceuticals previously exempted from environmental risk assessment may be added to the list for future assessment in response to advancements in the assessment technologies. A flexible assessment system should be constructed to allow quick and smooth response to introduction of new assessment technologies (leading to the addition of new endpoints) and addition of new target substances.

(2) Additional Information

When new information related to environmental risk becomes available for pharmaceuticals after completion of their examination, it should be notified to the regulatory authority and a notification system for such information should be developed within the framework of the environmental risk assessment system. Environmental risk assessment involves ecotoxicity tests conducted in a limited number of test species selected from diverse organism species on earth. Actually, however, the sensitivity of environmental organisms to ecotoxicity may vary from species to species. Consequently, new information on environmental risk in important also in view of ecosystem integrity as the goal of our national environmental policy.

(3) Existing Pharmaceuticals

While environmental risk assessment is required for new pharmaceuticals, those previously examined and approved are generally exempted from the assessment as "existing pharmaceuticals". However long-term exemption of existing pharmaceuticals from environmental risk assessment would enhance the gap from new pharmaceuticals and therefore may be considered to be unfair. In addition, self-reporting by the manufacturer alone is not satisfactory as a countermeasure for managing the environmental risk of existing chemical substances, as the history of the REACH system in EU has demonstrated. Therefore, exemption of existing pharmaceuticals from environmental risk assessment should be allowed only for a definite period, which should not be excessively long.

(4) Emission Control

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In contolling emission of pharmaceuticals into the environment, it would be desirable to implement effective measures by application of approaches generally used for chemical substances. Measures for preventing emission into the environment should be applied to unused and discarded pharmaceuticals as well. See Annex 10 for details of the proposed approaches for emission contol.

Concluding Remarks

Legislative measures for environmental impact assessment for pharmaceuticals have already been already implemented in major developed countries other than Japan. The obvious delay in coping with this problem observed in Japan cannot be overlooked, considering the slogan of the Japanese environmental policy of "a state founded on the principles of environmental protection". A concrete plan for measures to manage the environmental risk of pharmaceuticals in a manner most appropriate for the current situations in Japan should be established and implemented urgently, also taking international harmonization into account. The authors expect that the present report will serve as a good basis for accelerating implementation of environmental impact assessment for pharmaceuticals in Japan.

This study group was composed of experts with expertise in different fields. Individual group members participated in different parts of the study, based on their experience and knowledge. All of them participated in the overall discussion on all sections of this final report prior to completion of the final version. Investigators contributing to each section of this final report are listed below:

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Annex 1   The Concept of an Ecosystem

The basic concept of an ecosystem is explained for the schematic model of a lake (Fig. 4-1).[1] Various organisms living in a lake play mutually different roles in the construction of the ecosystem.   In general, organic compounds and nutrient salts (nitrogen, phophorus, etc.) are supplied to a lake from influent rivers and the atmosphere.   Phytoplanktons (the producers) grow by utilizing carbon dioxide and inorganic nutrient salts as the nutrient sources via the photosynthetic process.   Phytoplanktons (e.g., algae) serve as prey for smaller zooplanktons, such as Daphnia, while zooplanktons serve as prey for smaller fish. Larger fish (as well as some insect species and birds, like herons) prey on smaller fish and in turn, serve as prey for raptors (e.g., eagles, hawks, etc.).   Such interrelationship among organisms is designated as "food chain", which is closely related to migration and concentration of chemical substances.   Carcasses and excretory substances of these organisms are degraded by microorganisms (the degraders) into inorganic compounds. Some of them are dissolved in water and others sediment to the bottom of the lake to be returned again to the lake water as nutrient salts.   Thus, in the natural environment, close interrelationships exist among organisms and also between organisms and the surrounding non-biological environment.   An ecosystem is a material system consisting of biological communities and the inorganic environment, which is defined in The Convention on Biological Diversity as "a dynamic complex of plant, animal and microorganism communities and their non-living environment interacting as a functional unit"(Article 2).   Consequently, ecosystems in the aquatic environment of a river, a lake and sea are mutually different. Furthermore, ecosystems may change with the area, season, and time.   In brief, an ecosystem is dynamic in nature, both as an entity and as a concept.

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The Setting

Input from wastwater
or watershed

Input from atmosphere

Output

Birds

Attached organism and
large benthic plants

Phytoplankton → Zooplankton

Fish

Inorganic
nutrients

Bacteria

Organic compounds
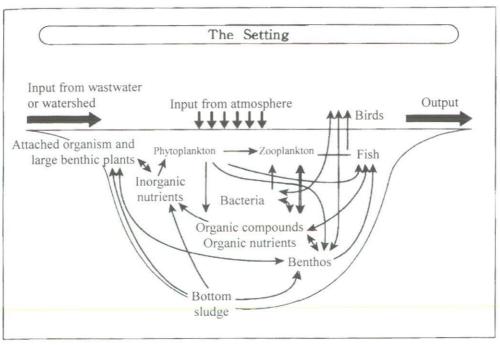Organic nutrients

Benthos

Bottom
sludge

Fig. 4-1.   Schematic Illustration of a Lake Ecosystem

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Annes 2. A list of OECD ecotxicity tests.

No.	Test species	Term (short, long)	Endpoints
201	Algae	72 h (short, long)	EC50;Growth inhibition[a]: MPD
202	Daphnia	48 h (short)	EC50;Immmobilizaion: MPD
203	Fish	96 h (short)	LC_{50};Death: MPD
204	Fish	14-21 d (short)	NOEC;Death,behavior,body length,body weight
205	Birds	5+3 d (short)	LC_{50}, NOEC;Death,symptom,behavior,body weight,food consumption
206	Birds	Parents: 8+(8-10) w (long), Young birds: 14 d	NOEC;Death,body weight,food consumption,pathological observations,egg production,number of abnormal eggs, egg shell thickness,effects on young birds (viability),incubation ratio
207	Earthworms	48 (72) h (Filter paper), 14 d (Soil) (short)	LC_{50};Death
208	Terrestrial plants	14-21 d after germination (short)	LC_{50};Germination, EC50;Growth
209	Activated suldge	0.5-3 h (short)	EC50; Respiration inhibition
210	Fish	30-60 d after hatching (long)	NOEC;Death,hatch,body length and body weight,abnormal behavior/morphology
211	Daphnia	21 d (long)	NOEC;Number of babyies (reproduction)
212	Fish	Egg to larva (short)	NOEC;Hatch,growth
213	Honeybees	48 h (-96 h) (short)	LD50;Death (oral),
214	Honeybees	48 h (-96 h) (short)	LD50;Death (contact toxicity)
215	Fish	28 d (juvenele fish)	ECx,NOEC;Growth rate
216	Microorganisms	28 d (-100 d)	ECx;N conversion
217	Microorganisms	28 d (-100 d)	ECx;C conversion
218 219	Bloodworm	20-65 d (long)	ECx,NOEC;Eclosion,death,growth (addition to bottom sediment) ECx,NOEC;Eclosion,death,growth (addition to upper-layer water)
220	Enchytraeina	6W-65 d (long)	ECx,NOEC;Propagation
221	Aquatic plants	7 d (duckweeds)	ECx,NOEC;Growth,propagation
222	Earthworms	4 W+4 W (soil)(Long)	ECx,NOEC;Propagation
223[b]	Birds	Acute oral toxicity (new)	
224	Anaerobic microorganisms	3 d	EC50 (gas production inhibition in anaerobic microorganisms for digestion treatment)
227	Terrestrial plants	21-28 d (short)	ECx,ERx,NOEC;Growth
c)	Birds	Parents:(2-14 W)+13-14 W, Young birds: 14 d (long)	NOEC;Injected in drinking water: Death,body weight,food consumption,pathological observations,egg production,number of abnormal eggs,egg shell thickness,viability of young birds,incubation ratio
c)	Fish	FI 150 d & FII 42 d (long)	ECx,NOEC;Death,growth,propagation,hatch

Note: Only three tests (No. 201, 210, and 211) are defined as long-term toxicity tests by OECD. The rest are tentatively classified by the Author.

a) Two toxicity values, short-term, and long-term, are obtained in a single test. b) Draft, c) Proposal only.

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Annex 3. Data required for regulatory uses of (Q)SAR

1) a defined endpoint
2) an unambiguous algorithm
3) a defined domain of applicability
4) appropriate measures of goodness-of-fit, robustness and predictivity
5) a mechanistic interpretation, if possible

Annex 4. A/C ratio

The value of the Uncertainty factor (UF) used to estimate the PNOE may be determined in some cases by considering the value of the acute-chronic ratio (ACR) in each test species (The Chemical Substances Control Law uses UF calculating considering the ACR).

ACRs have been reported for various chemical substances and in different test species.[1] Some examples are given below:

Tabata[2] determined the ACR values using 48-96 h LC_{50} of chemical substances and metals in fish and the limit concentration for chronic toxicity. Over 80% of the 32 target substances had ACR values below 100. In contrast, methyl mercury and kepone showed extremely high ACR values, in excess of 1000.

Kenega[3] calculated the ACR values for 135 chemical substances in 9 fishes and 2 crustacean species. An ACR value below 5 was observed for about 30% of the target substances, values below 10 were observed for about 40%, values below 25 were observed for about 67%, and values below 125 were observed for about 90% of the substances.

In Germany, Hegar[4] determined the ACR values for various new and existing chemical substances, as well as for pesticides in fish and Daphnia. For new chemical substances in fishes, ACR values below 10 were observed for 60% and values between 10 and 100 were observed for 20% of the substances; in Daphnia, ACR values below 10 were observed for 44% of the substances and values between 10 and 100 were observed for 36% of the substances. In either test species, ACR values below 100 were observed for 80% of the target substances. For existing chemical substances in Daphnia, ACR values below 10 were observed for 29% of the substances and values between 10 and 100 were observed for 53% of the substances. Thus, ACR values below 100 were observed for over 90% of the target substances.

Matsuzaki et al.[5] compared the ACR values determined by OECD toxicity tests in fishes, Daphnia and algae, mainly based on the data accumulated by The Ministry of Environment, Japan. Data for fishes alone were obtained from the AQUIRE database managed by EPA. In regard to the ACR values in fishes, values below 10 were observed for about 60% of the target substances, and values between 10 to 100 for 30% of the substances, and values of over 100 were observed for about 10% of the substances. In regard to the ACR values in Daphnia, values below 10 were observed for about 43% of the target substances, and values between 10 and 100 were observed for 47% of the substances. As a result, ACR values below 100 were observed for about 90% of the target substances. Conversely, ACR values above 100 were observed for 14 substances, most of which were aliphatic and aromatic amines. In algae, ACR was calculated by comparison of the EC50 and NOEC in a 72-h growth inhibition test. ACR values below 10 were observed for 92% of the target substances and the ACR values for all the substances examined were below 100.

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Webb et al.[6] surveyed the ACR values for pharmaceuticals obtained by Daphnia tests reported in 1998. The reported ACR values ranged from 1 to 1428, with a median of 43. The investigators pointed out that the observed distribution of the ACR values for pharmaceuticals in Daphnia was almost comparable with that for common industrial products in Crustacea. Table 4-3 summarizes the more recent data of ACR in 28 invertebrates (range, 1-29800; median 19.3).

As demonstrated above, ACR values vary very greatly depending on test species (test method) and target chemical substance. Under these circumstances, there are two alternative methods for determining the value for UF2: using the average ACR as the UF2, to set the UF2 value so as to cover the majority (e.g., 95%) of the observed ACR values. Which alternative to chose depends on the guideline for environmental impact assessment adopted. OECD uses the average ACR, while The Chemical Substances Control Law in Japan uses the value covering about 90% of ACR.

Table Annex 4.ACR values of pharmaceuticals in Crustacea

Drug efficacy class	Drug name	Test species	ACR
Antidepressant	Citalopram	*Ceriodaphnia dubia*	4.9
	Fluoxetine	*Ceriodaphnia dubia*	5.7
	Fluvoxamine	*Ceriodaphnia dubia*	2.3
	Paroxetine	*Ceriodaphnia dubia*	2.8
	Sertraline	*Ceriodaphnia dubia*	13.3
Anticpileptic	Carbamazepine	*Ceriodaphnia dubia*	3108
Antihyperlipoproteinemic	Clofibric acid	*Ceriodaphnia dubia*	>312
		Daphnia magna	1428
Bone resorption inhibitor	Etidronic acid	*Daphnia magna*	43.9
Cholinergic agonist	Nicotine	*Daphnia pulex*	42.9
Nonsteroid anti-inflammatory drug	Diclofenac	*Ceriodaphnia dubia*	22.7
	Ibuprofen	*Planorbis carinatus*	1.68
	Gentisic acid	*Daphnia longispina*	1070
		Daphnia magna	1258
	o-hydroxyhippuric acid	*Daphnia longispina*	>21
		Daphnia magna	>9.7
	Salicylic acid	*Daphnia longispina*	205
		Daphnia magna	<195
Estrogen	Diethylstilbestrol	*Nitocra spinepes*	97
		Tisbe battagliai	<10
		Daphnia magna	17.6
	Ethinylestradiol	*Nitocra spinepes*	10.2
		Daphnia magna	570
	Oestradiol	*Nitocra spinepes*	10

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Topical keratolytic	Salicylic acid	*Daphnia magna*	5.9
X-ray contrast medium	Iopromide	*Daphnia magna*	1
β-adrenergic receptor blocker	Propranolol	*Hyalella azteca*	29800
		Ceriodaphnia dubia	6.8

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Annex 5. Extrapolation Involving a Statistical Approach

When only a small number of test data are available for a combination of toxicity tests involving multiple test species, the smallest toxicity value obtained is often used for estimation of the PNEC to be on the safe side.   In contrast, when the number of data sets available is greater (i.e.,when toxicity data are availabe from a greater number of test species), the 5th percentile value can be calculated by applying a statistical theory to the obtained data and used to estimate the PNEC.   Ignoring the 5% is justified on the basis of the idea that, except for endangered species or some species with a high economic or social value, the effects of the target chemical substance on individual populations do not always matter seriously so far as the ecological role of a particular population can be taken over by some other species in the same ecosystem.   In particular, ecosystems in the aquatic environments in temperate regions have high functional redundancy (i.e., there are multiple species that share an identical ecological role in the ecosystem).   Such ecosystems are especially suitable for application of statistical extrapolation.

1) Hazardous concentration (HC$_5$)

Assuming a logarithmic logistic distribution or logarithmic normal distribution for NOEC, a hazardous concentration (HCp) to p% of organism can be estimated statistically. P=5% is usually used.   This approach can be used when the NOEC is available from five or more test species (note that the basic data set specified in most guidelines for environmental impact assessment involve three different test species).   First, whether the obtained data are extracted from the assumed probability distribution is confirmed by an appropriate statistical test.   Then HCp is calculated by using the following equation:

$$HCp = \frac{\overline{NOEC}}{T} \qquad T = e^{Sm \cdot k}$$

Where $\overline{NOEC}$ is the geometric mean of NOEC values obtained in different test species, m is the number of test species, Sm is the standard deviation of ln(NOEC) values obtained in m test species, p is the fraction of species not protected, and K is the limit factor for 1-tailed test in logistic or normal distribution.

HCp greatly depends on the magnitude of deviation of the sensitivity of the test species. The greater the deviation greater the uncertainty factor would be, yielding an unrealistically low HCp value.

2) Final chronic value (FCV)

Final chronic value (FCV) is defined as an estimate of the concentration related to the

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possibility of accumulation at P=0.05 for chronic toxicity observed in the genera tested. FCV is calculated on the basis of the NOEC values obtained from at least 8 test species belonging to 8 different genera.   The test genera have to include the following:

1)   Osteichthyes, Salmonidae
2)   Osteichthyes, other than Salmonidae (preferably warm water fish of commercial or recreationaly importance)
3)   Phylum Chordata
4)   Crustacean plankton
5)   Benthic crustacea
6)   Insects
7)   Phylum Arthropoda or pylum other than Chordata (e.g., Rotifera, Annelida, Mollusca, etc.)
8)   Other insects or animal phylum not listed above

Multiple chronic toxicity values obtained in an identical genus are represented by the geometric mean chronic value (GMCV).   From the cumulative distribution of GMCV, the lower 5th percentile value is derived using the lowest four GMCV values.   FCV is derived from the following equation:

$$FCV = e^{S \bullet \sqrt{0.05} + L} \qquad L = \frac{\sum (\ln GMCV) - S \bullet \sum \sqrt{P}}{4} \qquad S = \sqrt{\frac{\sum (\ln GMCV)^2 - \frac{(\sum \ln GMCV)^2}{4}}{\sum P - \frac{(\sum \sqrt{P})^2}{4}}}$$

Where GMCV is the geometric mean chronic value for one test genus, S is the standard deviation of lnGMCV versus number of test genera, N is the number of GMCV calculated, and P represents the possibility of accumulation of each GMCV value.   Calculated as P=R/(N+1), with R=1-4(or N) assigned to each of the lowest 4 GMCV values in ascending order.

HCp and FCV values obtained thus can be used as equivalents of PNEC.   Computer programs for calculation of these parameters are currently available.

Annex 6. Mulitple Pharmaceutical Products with Identical Mechanisms of Action

For pharmaceuticals, the mechanisms of actions in the human body by which they exert their biological activities are known in principle. Since there may be many pharmaceuticals exhibiting identical efficacies based on identical mechanisms of action, their overall environmental impacts are assumed and there remains the concern that the environmental impact assessment, unless conducted separately for each of these products, may not be sufficient to secure environmental safety.

Interaction between multiple substances may take the form of additive, synergistic, and antagonist actions. Basically, it would be most appropriate to assume additivity of actions for pharmaceuticals with identical mechanisms of action. Although synergistic toxicity may be observed for inhibitors of drug metabolism or transporters, such a situation is likely to be rather rare, except for those substances that are susceptible to bioaccumlation, considering that the Ki values for inhibitors are generally higher than their concentrations in the environment. A similar argument is likely to be valid in the case of synergistic toxicity due to interaction occurring at the site of action. In general, it would be desirable to collect data in greater detail if a synergistic action is suspected from a consideration of the characteristics of both the drug and environmental organisms.

What is needed under these circumstances is to sum up the emission volumes of the pharmaceuticals into the environment for each group classified by the mechanism of action, to multiply the potency or activity of each product by its emission volume, and finally take the total sum of contribution by each pharmaceutical product for control of the overall impact. More specifically, the concept of toxicity equivalent quantity (TEQ) applied to environmental impact assessment for dioxins appears to be useful: the toxicity of pharmaceutical products each having an identical mechanism of action is graded by comparison with that of a reference product (for which toxicity data have been accumulated most extensively among those belonging to this group) and numerical expression of the relative toxicity to the reference product as the value of the "toxicity equivalent factor (TEF)" assigned to each product.

In application of TEQ-based control to the environmental impacts of pharmaceuticals, the following should be kept in mind:

1) Target pharmaceuticals with identical mechanisms of action should be grouped together in advance.

2) TEF for each pharmaceutical product is calculated on the basis of comparative data on the actions in the target species and dynamics in the environment. When such data are not available, comparative data obtained either in vitro or in any of the organ, tissue, cellular,

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and subcellular levels should be consulted.

3) Drug classification and dose standards in the ATC/DDD published by the WHO provides a good reference.

4) For pharmaceuticals with an inhibitory activity on drug metabolism or transporters, the Ki values determined in vitro should be compared with such parameters as emission concentrations, environmental concentrations, and estimated accumulation concentrations in the target organism. If the former is below or comparable to the latter, special consideration is needed in controlling their envionmental impacts.

The following issues should also be taken into consideration:

1) There may be substantial interspecies differences in the development of toxicity. The ratio of the therapeutic or effective concentration of one drug to that of another observed in humans and laboratory animals may not always be identical with that in the target environmental organism. In examination of the impacts of pharmaceuticals on environmental ecosystems, it would be appropriate to limit the scope of assessment exclusively to impacts of a single chemical substance, as in examination of new chemical substances under The Chemical Substances Control Law in Japan.

2) Not all pharmaceuticals have a single point of action. It is not unusual for one pharmaceutical product to have two or more points of action. In such cases, it is usual to consider the main action (developing at the lowest concentration) first. However, if the target pharmaceutical product has another action potentially leading to some serious impact(s), top priority in examination and control should be given to this action.

3) In some cases with two drugs acting on an identical receptor, each may act as agonist when used alone, but as an antagonist to the other when used in combination. Such mutual cancellation of effect does not matter in the assessment on the safe side.

4) A possibility of synergistic toxicity exists between two pharmaceuticals.

5) Although it is true that examination of impacts caused by drug metabolites may be needed depending on the case, TEQ based on the TEF can be used as an index of the effectivenes of the entire process in the control of the environmental impacts of pharmaceuticals.

As discussed above, assuming that the mechanism of actions observed in human is also applicable to environmental organisms and the mechanism of toxicity development is dependent on the biological activity of the drug substance as well as its mechanism of action, ecotoxicity assessment based on a concept close to that of total emission control may be possible for pharmaceuticals with identical mechanisms of action.

Annex 7. Multiple Impacts Caused by Multiple Pollutants

The aquatic environment is generally polluted by multiple pollutants. When multiple substances coexist, toxicity may be decreased by interaction in some cases, but increased in an additive or synergistic manner in other cases.

Interaction between the toxicities of coexisting detergents and copper ion has been investigated.[1] Additive enhancement of toxicity has been reported between coexisting copper ions and anionic detergents, but no such effect has been observed between nonionic detergents and copper ions. When the concentrations of organophosphorus pesticides contained in river water flowing into the Tokyo metropolitan area and causing immobilization of Daphnia were investigated, the concentration of each pesticide product coexisting in the river water was, in most cases, below the level required to immobilize Daphnia when tested alone.[2] Further investigation of the relationship between the concentrations of the pesticides in river water and the concentration of each pesticide causing Daphnia immobilizaion demonstrated an additive interaction of the toxicity of some organophosphorus pesticides.[3] In contrast, fumic acid with its chelating activity may reduce the toxicity of heavy metals.[4]

As described above, although the effects of coexistence of multiple chemical substances on their actions have been investigated and conclusions on presence or absence of such effects have been reached for a number of combinations tested, currently available information is too limited to devise a systematic approach that might be generally applicable to this subject.